JC10 Rec'd PCT/PTO 02 JAN 2002

FORM PTO-1390 (Modified) (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	051023-0111

		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)
		Unassigned 10/019652
INTERNATIONAL APPLICATION NO. PCT/US00/17868	INTERNATIONAL FILING DATE 28 July 2000	PRIORITY DATE CLAIMED 28 July 1999

TITLE OF INVENTION
UREA DERIVATIVES AS INHIBITORS FOR CCR-3 RECEPTOR

APPLICANT(S) FOR DO/EO/US
Janak Padia, Michael D. Hocker, Tsuyoshi Nishitoba, Hiroshi Ohashi, and Eiji Sawa

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ has been transmitted by the International Bureau.
   - ☒ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. ☐ Applicant claims small entity status under 37 CFR 1.27 .

Items 12. to 17. below concern other document(s) or information included:

12. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
14. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ Other items or information: Application Data Sheet

10019652.020202

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U.S. APPLICATION NO (If known, see 37 CFR 1.5) Unassigned 10/019652	INTERNATIONAL APPLICATION NO PCT/US00/17868	ATTORNEY'S DOCKET NUMBER 051023-0111

18. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO.....$890.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2).....$740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO..... $1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))		

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate		
Total Claims	34	-	20	=	14	×	$18.00	$252.00	
Independent Claims	1	-	3	=	0	×	$84.00	$0.00	
Multiple dependent claim(s) (if applicable)							$280.00		
TOTAL OF ABOVE CALCULATIONS =								$1,142.00	
Reduction by ½ for filing by small entity, if applicable.								$0.00	
SUBTOTAL =								$1,142.00	
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +									
TOTAL NATIONAL FEE =								$1,142.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +									
TOTAL FEES ENCLOSED =								$1,142.00	
							Amount to be: refunded	$	
							charged	$	

a. ☒ A check in the amount of $1,142.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $0.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

FOLEY & LARDNER
Customer Number: 22428

22428

PATENT TRADEMARK OFFICE
Telephone: (202) 672-5407
Facsimile: (202) 672-5399

SIGNATURE

NAME STEPHEN A. BENT

REGISTRATION NUMBER 29,768

UREA DERIVATIVES AS INHIBITORS OF CCR-3 RECEPTOR

BACKGROUND OF THE INVENTION

The present invention relates to certain urea derivatives that are inhibitors of CCR-3 receptor activity, methods for preparing these compounds, pharmaceutical compositions containing such compounds and methods for their use.

Chemokines are chemotactic cytokines that are produced by a variety of cells to attract leukocytes to sites of inflammation or lymphoid tissue. CCR-3 is a chemokine receptor that is expressed in a variety of cells, including, but not limited to, eosinophils, basophils, T cells and dendritic cells. See Ponath, P.D. *et al.*, *J. Exp. Med.* (1996) 183, 2437-2448; Yamada, H. *et al.*, *Biochem. Biophys. Res. Comm.* (1997) 231, 365-368; Sallusto, F. *et al.*, *Science* (1997) 277, 2005-2007; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. CCR-3 is also known as a co-receptor to HIV virus infection. See He, J. *et al.*, *Nature* (1997) 385, 645-649. Several chemokines including eotaxin, eotaxin-2, RANTES, MCP-2, MCP-3, MCP-4 bind to CCR-3 and activate cell functions such as intracellular Ca^{2+} mobilization, chemotactic response, superoxide anion generation and cell aggregation. See Forssmann, U. *et al.*, *J. Exp. Med.* (1997) 185, 2171-2176; Heath, H. *et al.*, *J. Clin. Invest.* (1997) 99, 178-184; Uguccioni, M. *et al.*, *J. Exp. Med.* (1996) 183, 2379-2384; Tenscher, K. *et al.*, *Blood* (1996) 88, 3195-3199; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. In particular, eotaxin exhibits a potent and specific chemotactic activity for eosinophils via binding to CCR-3, *in vitro* and *in vivo*. See Ponath, P. D. *et al.*, *J. Clin. Invest.* (1996) 97, 604-612.

Tissue eosinophilia is observed in a number of pathological conditions such as asthma, rhinitis, eczema, inflammatory bowel diseases and parasitic infections. See Bousquest J. *et al.*, *N. Eng. J. Med.* 323, 1033-1039; Middleton, Jr., E. *et al.*, Chapter 42, Allergy Principles and Practice 4th ed. vol.2 Mosby-Year Book, Inc. 1993 U.S.A. In asthma, the airways of patients are infiltrated by a large numbers of eosinophils, and eotaxin production in bronchial mucosa and bronchoalveolar lavage (BALF) is increased.

Several studies have suggested a strong correlation between the number of eosinophils in BALF, the eotaxin level in BALF and the clinical parameters of disease severity. See Walker, C. *et al.*, *J. Allergy Clin. Immunol.* (1991) 88, 935-942; Ying, S. *et al.*, *Eur. J. Immunol.* (1997) 27, 3507-3516. Furthermore, pretreatment with a CCR-3-antibody has been shown to block chemotaxis and Ca^{2+} influx induced by eotaxin, RANTES, MCP-3 or MCP-4, suggesting that most of the eosinophilic response to these chemokines in allergic and eosinophilic patients is mediated through CCR-3. See Heath, H. *et al.*, *J. Clin. Invest.* (1997) 99, 178-184. Similarly, it has recently been disclosed that certain cyclic amine derivatives are antagonistic to CCR-3 and may be useful for treating eosinophil-mediated allergic diseases. See EP 0903349A2. Also, CCR-3 expression on human Th2 type T-cells and human cultured dendritic cells mediates cell functions such as chemotactic response. See Sallusto, F. *et al.*, *Science* (1997) 277, 2005-2007; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. In addition, anti-CCR-3 antibody has been shown to inhibit aggregation of T-cells and dendritic cells, suggesting CCR-3 may regulate the interaction of these cells during the process of antigen presentation. See Sato, K. *et al.*, *Blood* (1999) 93, 34-42. Therefore, CCR-3 inhibitors may also be useful for regulating immune responses.

These examples suggest that CCR-3 mediated diseases may be treated using compounds that inhibit CCR-3 activity. Because CCR-3 is present on many cell types, however, and is responsible for a variety of disease states, an arsenal of compounds which inhibit CCR-3 activity is required to treat CCR-3 mediated diseases effectively.

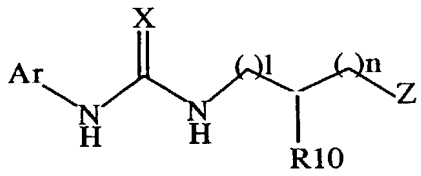
SUMMARY OF THE INVENTION

It is therefore one object of the present invention to provide compounds which inhibit CCR-3 receptor activity.

It is another object of the present invention to provide a method of treating CCR-3 mediated diseases.

In accomplishing these and other objects of the invention, there is provided, in accordance with one aspect of the present invention, a compound having the following

Formula:



or a salt, hydrate, or complex thereof, wherein:

l and n are independently 0, 1, 2, 3, 4 or 5;

(l + n) is 1, 2, 3, 4 or 5;

X is O or S;

R10 is selected from the group consisting of hydrogen, hydroxy, C_{3-7}cycloalkyloxy, acyloxy, carboxy, carbamoyl, acyl, amino, alkylamino, arylamino, acylamino, C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl, alkyloxycarbonyl,

Wherein the C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl or alkyloxycarbonyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, acyloxy, C_{1-5}alkoxy, aryloxy, heteroaryloxy, nitro, amino, acylamino, alkylamino, arylamino, cyano, aryl, heteroaryl

Wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-5}alkyl or C_{1-5}alkoxy, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydroxy, and halogen;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl,

carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

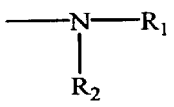
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

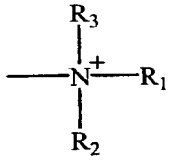
and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

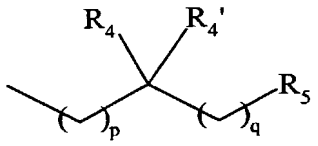
Z is:



or



wherein R_1 is:



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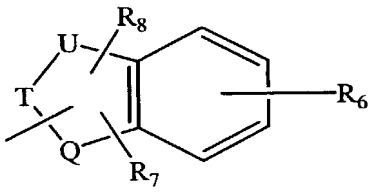

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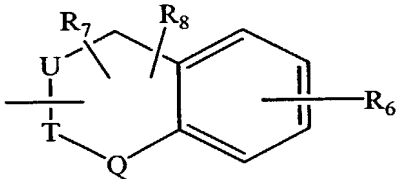
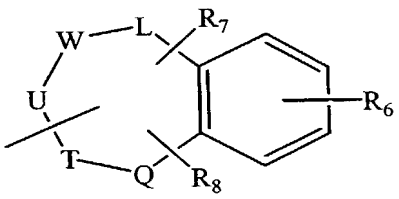


or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl,

isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido,

arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

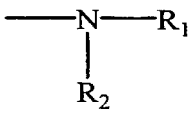
C_{3-7} cycloalkyl

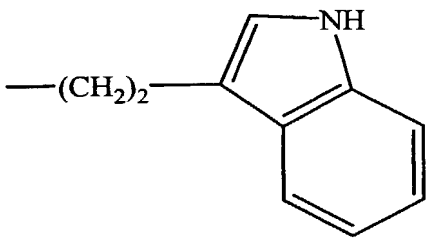
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

further provided that Ar is not 2-hydroxy-5-methoxyphenyl, and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not .

In another embodiment of the present invention, there is provided a pharmaceutical composition comprising one or more the disclosed compounds.

In yet another embodiment, there is provided a method of treating CCR-3 mediated diseases in a patient, comprising administering to the patient an effective amount of a pharmaceutical composition comprising one or more of the inventive compounds of the present invention.

In another embodiment, a kit is provided for treating CCR-3 mediated diseases in a patient, comprising:

(A) a pharmaceutical composition comprising one or more of the inventive compounds of the present invention;

(B) reagents to effect administration of the pharmaceutical composition to the patient; and

(C) instruments to effect administration of the pharmaceutical composition to the patient.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood that examples are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Scheme 1 provides a schematic representation of the synthesis of N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound No.1).

Scheme 2 provides a schematic representation of the synthesis of N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-propyl-1,3-diaminopropane (Compound No.10).

Scheme 3 depicts the synthesis of Methyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound No. 29).

Scheme 4 depicts the synthesis of 4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound No.60).

Scheme 5 depicts the synthesis of [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl]-diethylammonium iodide (Compound No.91).

Scheme 6 depicts the synthesis of Active Compounds by Solid Phase Synthesis.

Scheme 7 depicts the synthesis of N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl 2-hydroxy-1,3-diaminopropane (Compound No.163).

Scheme 8 depicts the synthesis of 4-[[3-(4-chlorophenylthioureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound No.164).

Scheme 9 depicts the synthesis of 4-[[(3*S*)-3-(4-bromophenylureido)-3-(*tert*-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound Nos.165 and 166).

Scheme 10 depicts the synthesis of 4-[[3-(4-bromophenylureido)-2-hydroxypropyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound No.167).

Scheme 11 depicts the synthesis of 4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanamide (Compound No.193).

Scheme 12 depicts the synthesis of 3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[(phenylsulfonyl)carbamoyl]propane (Compound No.196).

Scheme 13 depicts the synthesis of 4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-butanol (Compound No.203).

Scheme 14 depicts the synthesis of 3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-(1*H*-tetrazol-5-yl)propane (Compound No.218).

Scheme 15 depicts the synthesis of Methyl 4-[[3-[4-(carboxy)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound No.225).

Scheme 16 depicts the synthesis of 4-[[3-[4-(Ethoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound No.228).

Scheme 17 depicts the synthesis of [3-(Phenylureido)propyl]bis[2-(4-chlorophenyl)ethyl]amine (Compound No.238).

Scheme 18 depicts the synthesis of 4-[[(3*S*)-3-(4-Bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound No.286).

Scheme 19 depicts the synthesis of [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl]bis(4-methylbenzyl)ammonium iodide (Compound No.296).

Scheme 20 depicts the synthesis of [3-(4-Bromophenylureido)propyl][(1*S*)-1-phenylethyl][3-(carboxy)propyl]ethylammonium trifluoroacetate (Compound No.315).

Scheme 21 depicts the synthesis of [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(carboxy)benzyl]ethylammonium iodide (Compound No.322).

Figure 1A demonstrates the inhibitory effects of Compound No. 60 on collagen-induced arthritis.

Figure 1B demonstrates the inhibitory effects of Compound No. 298 on collagen-induced arthritis.

Figure 2A shows the dose-response curves of bronchoconstriction against acetylcholine (murine asthma model) with and without treatment of compound No. 298.

Figure 2B shows the area under each of the dose-response curves of Figure 2A.

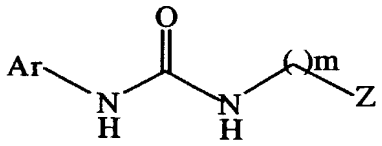
Figure 2C shows the suppression of compound No. 298 (CPD No. 298) on eosinophil infiltration to bronchoalveolar lavage fluid (BALF). Two hundred cells were counted in each experiment.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a new class of compounds which inhibit CCR-3 receptor activity. Because the CCR-3 receptor is understood to mediate a variety of diseases, the disclosed compounds, which are derived from urea, are useful for treating CCR-3-mediated diseases. Examples of such diseases include, without limitation, eosinophil-mediated diseases such as asthma, rhinitis, eczema, inflammatory bowel diseases, parasitic infections, and diseases that are mediated by T-cells, mast cells (Ochi H. et al., *J. Exp. Med.* (1999) 190:267-280, Romagnani P. et al., *Am. J. Pathol.* (1999)

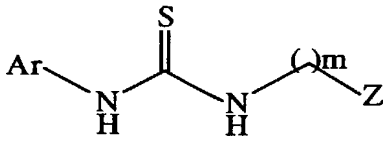
155:1195-1204) and/or dendritic cells, such as autoimmune and inflammatory diseases and HIV infection.

In one embodiment of the present invention, there is provided a variety of compounds that inhibit cell function mediated by the chemokine receptor CCR-3. In general, these compounds are either urea derivatives (Formula I) or thiourea derivatives (Formula III). Their formulas are depicted below:



(I)

and



(III)

The compounds of Formula (I) and (III), as defined above, include variable groups such as an aryl group, a heteroaryl group and a heterocyclic group.

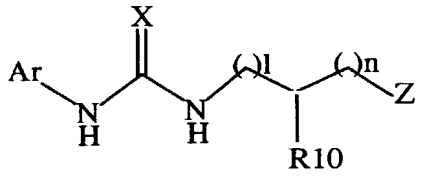
An aryl group is defined as a 6-15 membered aromatic carbocyclic moiety. This includes but is not limited to phenyl, naphthyl, anthryl, indenyl, phenanthrenyl and others.

A heteroaryl group is defined as a 5-15 membered aromatic ring system containing at least one hetero atom selected from the group consisting of N, O, and S. These include but are not limited to 2- or 3-thienyl, 2- or 3-furyl, 2- or 3- pyrrolyl, 2-, 3- or 4- pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5- thiazolyl, 3-, 4- or 5- pyrazolyl, 2-, 4- or 5- imidazolyl, 3-, 4- or 5- isoxazolyl, 3-, 4- or 5- isothiazolyl, 3- or 5- (1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5- (1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido- 2-, 3- or 4- pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido- 2-, 4- or 5- pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, triazinyl, oxotriazinyl, tetrazolo[1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl,

oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

A heterocyclic group is defined as a 5-15 membered non-aromatic ring system containing at least one hetero atom selected from the group consisting of N, O, and S. These include but are not limited to hydrogenated derivatives of 2- or 3-thienyl, 2- or 3-furyl, 2- or 3- pyrrolyl, 2-, 3- or 4- pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5- thiazolyl, 3-, 4- or 5- pyrazolyl, 2-, 4- or 5- imidazolyl, 3-, 4- or 5- isoxazolyl, 3-, 4- or 5- isothiazolyl, 3- or 5- (1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5- (1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido- 2-, 3- or 4- pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido- 2-, 4- or 5- pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, triazinyl, oxotriazinyl, tetrazolo [1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, phenazinyl, phenothiazinyl and phenoxazinyl. The heterocyclic moiety may also include dioxolanyl, morpholinyl, piperidinyl, and piperazinyl.

In another embodiment of the present invention, there is provided another family of compounds which inhibit cell function mediated by the chemokine receptor CCR-3. In general, these compounds have the Formula (II) depicted below:



(II)

or a salt, hydrate, or complex thereof, wherein:

l and n are independently 0, 1, 2, 3, 4 or 5;

(l + n) is 1, 2, 3, 4 or 5;

X is O or S;

R10 is selected from the group consisting of hydrogen, hydroxy, C_{3-7}cycloalkyloxy, acyloxy, carboxy, carbamoyl, acyl, amino, alkylamino, arylamino, acylamino, C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl, alkyloxycarbonyl,

Wherein the C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl or alkyloxycarbonyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, acyloxy, C_{1-5}alkoxy, aryloxy, heteroaryloxy, nitro, amino, acylamino, alkylamino, arylamino, cyano, aryl, heteroaryl

Wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-5}alkyl or C_{1-5}alkoxy, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydroxy, and halogen;

Ar may be aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide,

arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

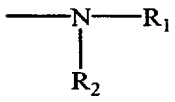
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Z may be



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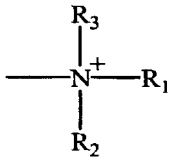
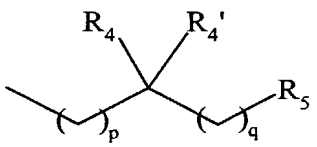
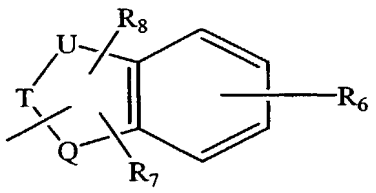


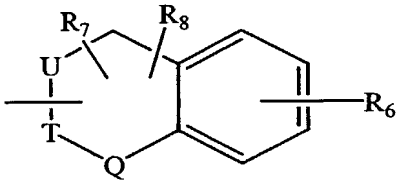
wherein R_1 is:



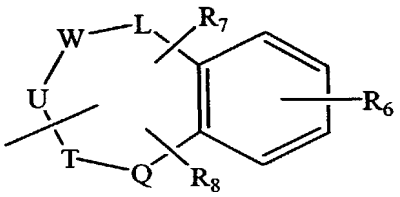
or



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy,

sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

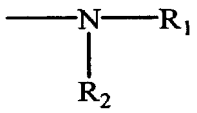
C_{3-7} cycloalkyl

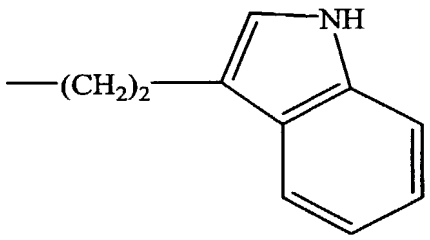
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

further provided that Ar is not 2-hydroxy-5-methoxyphenyl, and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not .

The compounds of the present invention can be prepared by various methods including, but not limited to, liquid phase or a solvent based synthesis and solid phase synthesis involving a polymeric resin.

The liquid phase synthesis generally involves addition of a substituted or unsubstituted alkyl amine containing compound to a protected amine containing starting material bearing a leaving group (e.g., Cl, Br, I, OTs, OMs, etc.). The resulting product bearing a protonated amine is reacted with an alkyl halide to yield a substituted amine. Then, the protected amine moiety is deprotected by addition of base or e.g., hydrazine.

The resultant free amine is reacted with a compound containing an aromatic isocyanate to yield the aromatic urea derivative.

A second synthesis involves the reaction of aromatic isocyanate with a haloalkylamine. The resultant product is then further reacted with an optionally substituted amine containing compound, the amine of the optionally substituted amine containing compound is substituted by reaction with an alkyl halide to yield the aromatic urea derivative.

An additional method that can be used to prepare the present compounds involves reaction of a protected amine containing starting compound with an alkylamine. The resultant diamine is reacted with an ester containing a leaving group, after deprotection, the aromatic urea derivative is formed by reaction with a compound containing an aromatic isocyanate.

The aromatic urea derivatives can be further derivatized by conventional organic synthesis techniques, for example, an ester can be converted to an acid by addition of a metal hydroxide. Additionally, salts of the compounds can be formed by conventional synthetic techniques, such as addition to an amine moiety to form an ammonium salt.

Solid phase synthesis involves the use of polymeric resins. Reductive amination of the linker to the resin occurs by reacting a haloalkylamine with the polymeric resin. The protonated amine is then protected by reaction with a substituted or unsubstituted acid chloride. The halogen of the original haloalkylamine is displaced by reaction with an alkyl amine compound and reductive amination follows by reaction with an aldehyde. The protected amine is deprotected by reaction with, for example, tin chloride, an acid or an amine. The deprotected amine is subsequently reacted with an isocyanate to yield the urea moiety, the product is isolated by working up the reaction mixture, for example, in HCl gas.

In one embodiment of the present invention, an effective amount of a pharmaceutical composition comprising one or more of the disclosed compounds is administered to a patient suffering from CCR-3 mediated disease. The active compound of the pharmaceutical composition can be administered in a variety of forms, including, but not limited to a salt, a hydrate or a prodrug. In addition, the pharmaceutical composition can optionally contain suitable carriers or excipients.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts, hydrates or prodrugs thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

A "prodrug" refers to an agent which is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug.

As used herein, a "physiologically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

An "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples of excipients include, but are not limited to, calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, vegetable oils and polyethylene glycol.

The form of the administered compound depends, in part, upon the use or the route of entry. Such forms should allow the agent to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological agents or compositions injected into the blood stream should be soluble in the concentrations used. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the compound or composition from exerting its effect.

A compound of the present invention also can be formulated as a pharmaceutically acceptable salt, e.g., acid addition salt, and complexes thereof. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the agent without preventing its physiological effect. Examples of useful alterations in physical properties include, but are not limited to, lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

A compound of the present invention can be administered to a mammal, including a human patient, using a variety of techniques. For example, for systemic administration,

oral administration or injection can be used. For oral administration, a compound of the present invention is formulated into conventional oral administration dosage forms such as capsules, tablets, and tonics. For injection, a compound is formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, a compound can be formulated in a solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced. Examples of systemic administrations by injection include intramuscularly, intravenously, intraperitoneally and subcutaneously.

Administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration also can be achieved, for example, by using nasal sprays or suppositories.

Administration of a compound of the present invention can be achieved by any means which transports the compound to the airways and/or lungs of a mammal, including a human patient. In a preferred embodiment, a compound is administered by generating an aerosol comprised of respirable particles, comprising said compound. Delivery is achieved by animal or patient inhalation of the respirable particles. The respirable particles can be liquid or solid and, optionally, can contain other therapeutic ingredients.

For topical administration, the molecules of the invention are formulated into ointments, salves, gels, or creams, as is generally known in the art.

Generally, a therapeutically effective amount for a human patient is between about 10 nmole and 3 mmole of the compound, preferably 1 μmole to 1 mmole. A therapeutically effective amount for a non-human mammal is between about 0.01 and 50 mg/kg, preferably 0.01 and 20 mg/kg. Optimization of the timing and dosage of a disclosed compound is by convention adapted to, among other things, the particular characteristics of the patient or the non-human mammal and the nature and extent of the disease state, and the EC50 or IC50 of the compound. Such adaptations are routine and do not require abnormal experimentation or skill in the art.

In accordance with yet another aspect of the present invention, there is provided a kit suitable for treating CCR-3 mediated diseases in a patient, comprising a pharmaceutical

composition comprising one or more compounds of the present invention, reagents to effect administration of the pharmaceutical composition to the patient and instruments to effect administration of the pharmaceutical composition to the patient. Examples of such instruments include, but are not limited to application devices, such as syringes or inhalers.

In yet another emobobyment, the claimed compounds are useful for treatment and/or prevention of rheumatoid arthritis. The treatment includes, but not limited to, administration of the claimed compounds through subcacutaneous, intradermal, intramuscular, intraperitoneal, intravascular, and intracranial injections to human or other mammalian animal bodies.

EXAMPLES:

SYNTHESIS OF ACTIVE COMPOUNDS

Example 1. Synthesis of N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound 1)

The following synthesis is depicted in Scheme 1.

Step 1: To a mixture of 2-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in CH_3CN (50 ml) was added N-(3-bromopropyl)phthalimide (3.0 g, 11 mmol). The mixture was refluxed under stirring for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 67%): MS(FD) m/e 343 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.74 (d, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.84 (m, 2H).

Step 2: To a mixture of N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 6.65 mmol) and potassium carbonate (1.8 g, 13 mmol) in CH_3CN (50 ml) was added ethyl iodide (1.6 ml, 20 mmol). The mixture was stirred at 70 °C for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2% methanol/chloroform) to afford N-[3-[[2-(4-chlorophenyl)ethyl](ethyl)amino]propyl]phthalimide (1.41 g, 57%): MS(ES^+) m/e 371 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 3.71 (t, J = 7.3 Hz, 2H), 2.66 (m, 4H), 2.57 (m, 4H), 1.83 (m, 2H), 1.00 (t, J = 7.1 Hz, 3H).

Step 3: To a solution of N-[3-[[2-(4-chlorophenyl)ethyl](ethyl)amino]propyl]-phthalimide (1.41 g, 3.8 mmol) in EtOH (20 ml) was added a solution of hydrazine monohydrate (1.5 g, 30 mmol) in EtOH (5 ml). The solution was stirred at RT for 4h, and then filtered. The filtrate was concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave N-[2-(4-chlorophenyl)ethyl]-N-ethyl-1,3-

diaminopropane (903 mg, 99%) which was used in the next step without further purification.

Step 4: To a solution of N-[2-(4-chlorophenyl)ethyl]-N-ethyl-1,3-diaminopropane (30 mg, 0.125 mmol) in CH_2Cl_2 (1 ml) was added phenyl isocyanate (18 mg, 0.15 mmol). After stirring at RT for 1h, the reaction mixture was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (38.7 mg, 86%): MS(ES^+) m/e 360 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 6H), 7.08 (d, J = 8.3 Hz, 2H), 7.03 (m, 1H), 6.93 (br, 2H), 3.34 (m, 2H), 2.76-2.70 (m, 8H), 1.76 (m, 2H), 1.08 (t, J = 7.1 Hz, 3H).

Compound 2, N-(4-Nitrophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(FD) m/e 405 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 9.3 Hz, 2H), 7.65 (br, 1H), 7.51 (d, J = 9.2 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.38 (br, 1H), 3.33 (m, 2H), 2.83 (m, 4H), 2.74 (m, 4H), 1.76 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H).

Compound 3, N-(4-Bromophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES^+) m/e 438 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.60 (br, 1H), 7.32 (d, J = 8.8, Hz, 2H), 7.26 (m, 4H), 7.08 (d, J = 8.3 Hz, 2H), 6.25 (br, 1H), 3.26 (t, J = 6.1 Hz, 2H), 2.73 (m, 8H), 1.71 (m, 2H), 1.08 (t, J = 7.3 Hz, 3H).

Compounds 4-9, 191, 192, 202, 204, 215, 230-234, 239-245, 274-276, 280, 291, 292 can be obtained in an analogous manner to that of Compound 1.

Example 2. Synthesis of N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-propyl-1,3-diaminopropane (Compound 10)

The following synthesis is depicted in Scheme 2.

Step 1: Phenyl isocyanate (1.4 ml, 13 mmol) was added to a solution of 3-bromopropylamine hydrobromide (2.5 g, 11 mmol) and triethylamine (1.7 ml, 12 mmol) in DMF (50 ml) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. After adding water, the mixture was extracted with ethyl acetate, washed with water and brine, dried over

sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% ethyl acetate/hexane to 50% ethyl acetate/hexane) to afford N-phenylcarbamoyl-3-bromopropylamine (2.7 g, 96%): MS(FD) m/e 256 M^+; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 4H), 7.11 (m, 1H), 6.45 (br, 2H), 3.46 (t, J = 6.3 Hz, 2H), 3.41 (t, J = 6.6 Hz, 2H), 2.10 (m, 2H).

Step 2: 2-(4-Chlorophenyl)ethylamine (1.8 g, 12 mmol) was added to a mixture of N-phenylcarbamoyl-3-bromopropylamine (2.5 g, 9.7 mmol) and potassium carbonate (2.6 g, 19 mmol) in CH_3CN (50 ml). The mixture was stirred at 70 °C for 4.5 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was dissolved with chloroform, washed with water, 1N-HCl and brine. The organic layer was dried over sodium sulfate, filtered, and then concentrated under vacuum to dryness. The residue was chromatographed on silica gel (eluting with 2% methanol/chloroform) to afford N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-1,3-diaminopropane (1.43 g, 45%): MS(ES^+) m/e 332 M^+; ^1H NMR (400 MHz, CD_3OD) δ7.35-7.15 (m, 8H), 6.99 (m, 1H), 3.31 (m, 2H), 3.23 (m, 2H), 3.06 (t, J = 7.1 Hz, 2H), 3.00 (m, 2H), 1.89 (m, 2H).

Step 3: Propyl iodide (51 mg, 0.30 mmol) was added to a mixture of N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-1,3-diaminopropane (33 mg, 0.10 mmol) and potassium carbonate (28 mg, 0.20 mmol) in CH_3CN (2 ml). The mixture was stirred at 75 °C for 5 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was purified by preparative normal phase HPLC using linear gradients of (A) chloroform and (B) methanol (0-5% B, in 0-10 min; 5-10% B, in 10-30 min; 10-15% B, in 30-40 min) at a flow rate of 10 ml/min. Fractions containing the major peak were pooled and concentrated to afford N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-propyl-1,3-diaminopropane (27 mg, 59%): MS(ES^+) m/e 374 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 2H), 7.25 (m, 4H), 7.07 (m, 3H), 5.98 (br, 1H), 5.00 (br, 1H), 3.31 (m, 2H), 2.78 (m, 6H), 2.59 (m, 2H), 1.76 (m, 2H), 1.52 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H).

Compounds 11-28, 219-221 can be obtained in an analogous manner to that of Compound 10.

Example 3. Synthesis of Methyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound 29)

The following synthesis is depicted in Scheme 3.

Step 1: N-(3-Bromopropyl)phthalimide (13.0 g, 48.5 mmol) was added to a mixture of 1,2,3,4-tetrahydro-1-naphthylamine (6.96 ml, 48.5 mmol) and potassium carbonate (13.4 g, 97.0 mmol) in CH_3CN (200 ml). The mixture was refluxed under stirring for 21 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 1.5% methanol/chloroform) to afford N-[3-(1,2,3,4-tetrahydro-1-naphthylamino)propyl]phthalimide (23.9 g, 74%): MS(ES^+) m/e 335 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.39 (m, 1H), 7.13 (m, 2H), 7.06 (m, 1H), 3.81 (m, 3H), 2.81 (m, 2H), 2.71 (m, 2H), 2.00-1.85 (m, 4H), 1.72 (m, 2H).

Step 2: Methyl 4-bromobutylate (16.3 g, 89.8 mmol) was added to a mixture of N-[3-(1,2,3,4-tetrahydro-1-naphthylamino)propyl]phthalimide (10.0 g, 29.9 mmol) and potassium carbonate (8.28 g, 59.9 mmol) in DMF (150 ml). The mixture was stirred at 130 °C for 22 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford methyl 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (4.62 g, 36%): MS(ES^+) m/e 435 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.63 (m, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.03 (m, 1H), 6.94 (m, 2H), 3.90 (m, 1H), 3.51 (m, 2H), 2.63 (m, 2H), 2.45-2.20 (m, 6H), 1.91 (m, 2H), 1.74 (m, 4H), 1.52 (m, 2H).

Step 3: Hydrazine monohydrate (1.03 ml, 21.3 mmol) was added to a solution of methyl 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (4.62 g, 10.6 mmol) in EtOH (80 ml) at 0 °C. After stirring at RT for 2h, additional hydrazine monohydrate (1.03 ml, 21.3 mmol) was added. The solution was stirred at RT for 2h, and concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. The filtrate was dissolved with chloroform, and then extracted with 1N-HCl. The water layer was neutralized with 1N-NaOH at 0 °C, washed with chloroform, and then basified with 1N-NaOH (pH = 14), extracted with chloroform. The organic layer was washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave methyl 4-[(3-aminopropyl)(1',2,3,4-

tetrahydro-1-naphthyl)amino]butylate (1.05 g, 33%) which was used in the next step without further purification.

Step 4: 4-Bromophenyl isocyanate (83 mg, 0.42 mmol) was added to a solution of methyl 4-[(3-aminopropyl)(1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (106 mg, 0.35 mmol) in CH_2Cl_2 (3 ml). After stirring at RT for 1h, the reaction mixture was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and the plate was developed with 6% methanol/chloroform to afford methyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (89 mg, 51%): MS(FD) m/e 502 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.50 (br, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.35 (m, 4H), 7.13-7.01 (m, 3H), 6.09 (t, J = 5.5 Hz, 1H), 3.89 (dd, J = 9.0, 5.1 Hz, 1H), 3.53 (s, 3H), 3.12 (m, 1H), 3.03 (m, 1H), 2.67 (m, 2H), 2.43-2.25 (m, 6H), 2.00-1.88 (m, 2H), 1.70-1.50 (m, 6H).

Compound 30, Methyl 4-[[3-(4-bromophenylureido)propyl][(1*R*)-1-phenylethyl]-amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES^+) m/e 476 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 1H), 7.38-7.21 (m, 8H), 7.08 (br, 1H), 5.47 (br, 1H), 3.91 (m, 1H), 3.65 (s, 3H), 3.20 (m, 2H), 2.49 (m, 3H), 2.29(m, 3H), 1.77 (m, 2H), 1.61 (m, 2H), 1.31 (d, J = 6.6 Hz, 3H).

Compound 31, Methyl 4-[[3-(4-bromophenylureido)propyl][2-(4-chlorophenyl)-ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES^+) m/e 510 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (br, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.25 (m, 4H), 7.08 (d, J = 8.3 Hz, 2H), 5.99 (br, 1H), 3.70 (s, 3H), 3.28 (t, J = 5.9 Hz, 2H), 2.68 (br, 4H), 2.59 (t, J = 5.9 Hz, 2H), 2.53 (t, J = 6.8 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 1.79 (m, 2H), 1.68 (m, 2H).

Compound 32, Methyl 4-[[4-(4-bromophenylureido)butyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES^+) m/e 516 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (br, 1H), 7.62 (m, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.10 (m, 2H), 7.03 (m, 1H), 5.37 (m, 1H), 3.89 (m, 1H), 3.66 (s, 3H), 3.17 (m, 2H), 2.70 (m, 2H), 2.51-2.29 (m, 6H), 1.96 (m, 2H), 1.76 (m, 2H), 1.68-1.40 (m, 6H).

Compound 33, Methyl 4-[[5-(4-bromophenylureido)pentyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 530 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.29 (br, 1H), 7.21 (d, J = 9.0 Hz, 2H), 7.09 (m, 2H), 7.02 (m, 1H), 5.31 (m, 1H), 3.90 (m, 1H), 3.66 (s, 3H), 3.20 (m, 2H), 2.71 (m, 2H), 2.49-2.27 (m, 6H), 1.97 (m, 2H), 1.76 (m, 2H), 1.60 (m, 2H), 1.43 (m, 4H), 1.27 (m, 2H).

Compound 34, Methyl 4-[[3-(4-methylphenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 438 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.21 (br, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.13-6.99 (m, 5H), 5.98 (t, J = 5.6 Hz, 1H), 3.90 (dd, J = 9.5, 4.9 Hz, 1H), 3.54 (s, 3H), 3.11 (m, 1H), 3.02 (m, 1H), 2.67 (m, 2H), 2.43-2.23 (m, 6H), 2.20 (s, 3H), 1.94 (m, 2H), 1.70-1.50 (m, 6H).

Compound 35, Methyl 4-[[3-(3,4-dichlorophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 492 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-*d6*) δ9.20 (br, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.28 (dd, J = 8.8, 2.4 Hz, 1H), 7.19-7.07 (m, 3H), 6.27 (m, 1H), 3.95 (m, 1H), 3.60 (s, 3H), 3.18 (m, 1H), 3.10 (m, 1H), 2.73 (m, 2H), 2.57-2.29 (m, 6H), 2.00 (m, 2H), 1.74-1.54 (m, 6H).

Compound 172, Methyl 4-[[3-(4-bromophenylureido)propyl](1-indanyl)amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 490 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.32 (bs, 1H), 7.43 (m, 1H), 7.30 (m, 2H), 7.26 (m, 2H), 7.20 (m, 3H), 5.77 (br, 1H), 4.50 (m, 1H), 3.65 (s, 3H), 3.27 (m, 2H), 2.82 (m, 2H), 2.51 (m, 1H), 2.40 (m, 4H), 2.31 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.81 (m, 2H), 1.66 (m, 2H).

Compound 178, Methyl 4-[[3-(4-bromophenylureido)propyl][(1*R*)-1-indanyl]amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 490 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.24 (br, 1H), 7.31 (m, 3H), 7.26 (m, 3H), 7.20 (m, 2H), 5.69

(br, 1H), 4.50 (t, J = 6.8 Hz, 1H), 3.66 (s, 3H), 3.28 (m, 2H), 2.90-2.77 (m, 2H), 2.52-2.26 (m, 6H), 2.05 (m, 1H), 1.95 (m, 1H), 1.81 (m, 2H), 1.66 (m, 2H).

Compound 180, Methyl 4-[[3-(4-bromophenylureido)propyl][(1*R*)-1,2,3,4-tetrahydro-1-naphthyl]amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 504 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.19 (br, 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.12 (m, 2H), 7.05 (d, J = 6.9 Hz, 1H), 5.43 (br, 1H), 3.95 (m, 1H), 3.66 (s, 3H), 3.24 (m, 2H), 2.70 (m, 2H), 2.55-2.36 (m, 5H), 2.27 (m, 1H), 1.94 (m, 2H), 1.79 (m, 2H), 1.62 (m, 4H).

Compound 184, Ethyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 29 and contains the following characteristics: MS(ES$^+$) m/e 516 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.54 (d, J = 7.3 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.09 (m, 2H), 7.01 (d, J = 6.8 Hz, 1H), 5.33 (br, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.98 (m, 1H), 3.26 (m, 1H), 3.20 (m, 1H), 2.65 (m, 2H), 2.61-2.31 (m, 5H), 2.22 (m, 1H), 1.91 (m, 2H), 1.74 (m, 2H), 1.60 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H).

Compounds 36-59, 174, 176, 182, 185, 187, 189, 194, 198, 200, 206, 208, 212, 213, 224 can be obtained in an analogous manner to that of Compound 29.

Example 4. Synthesis of 4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 60)

The following synthesis is depicted in Scheme 4.

Lithium hydroxide monohydrate (14 mg, 0.33 mmol) was added to a solution of methyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound 29, 83 mg, 0.17 mmol) in 10% water/methanol (2 ml). After stirring at RT for 16 h, additional lithium hydroxide monohydrate (14 mg, 0.33 mmol) was added. The reaction mixture was stirred at RT for 6 h, and then concentrated under vacuum to dryness. The residue was dissolved with ether and water, and partitioned. The water layer was acidified with 1N-HCl (pH = 1), extracted with ethyl acetate, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and the plate was developed with 17% methanol/chloroform to afford 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-

naphthyl)amino]butanoic acid (44 mg, 53%): MS(ES$^+$) m/e 488 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br, 1H), 8.76 (br, 1H), 7.72 (m, 1H), 7.38 (m, 4H), 7.23 (m, 3H), 6.35 (br, 1H), 4.92 (br, 1H), 2.97 (m, 2H), 2.85-2.65 (m, 8H), 2.18 (m, 2H), 2.00 (m, 2H), 1.67 (m, 4H).

Compound 61, 4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-phenylethyl]amino]-butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 462 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br, 1H), 7.50 (br, 1H), 7.40-7.25 (m, 9H), 6.90 (br, 1H), 4.31 (br, 1H), 3.23 (m, 2H), 2.50-2.21 (m, 6H), 1.74 (m, 4H), 1.27 (m, 3H).

Compound 62, 4-[[4-(4-Bromophenylureido)butyl](1,2,3,4-tetrahydro-1-naphthyl)-amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 502 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, J = 7.3 Hz, 1H), 7.38-7.24 (m, 7H), 5.01 (t, J = 7.5 Hz,1H), 3.20 (br, 2H), 2.92-2.76 (m, 4H), 2.45-2.29 (m, 4H), 2.04 (m, 4H), 1.87 (m, 2H), 1.75 (m, 2H), 1.53 (br, 2H).

Compound 63, 4-[[5-(4-Bromophenylureido)pentyl](1,2,3,4-tetrahydro-1-naphthyl)-amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 516 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, J = 7.1 Hz, 1H), 7.36-7.24 (m, 7H), 5.01 (t, J = 7.5 Hz, 1H), 3.17 (br, 2H), 2.91-2.76 (m, 4H), 2.45-2.28 (m, 4H), 2.04 (m, 4H), 1.84 (m, 2H), 1.75 (m, 2H), 1.51 (m, 2H), 1.35 (m, 2H).

Compound 64, 4-[[3-(4-Methylphenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)-amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 424 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-*d6*) δ9.29 (br, 1H), 8.31 (br, 1H), 7.67 (br, 1H), 7.25 (m, 4H), 7.02 (m, 3H), 6.15 (br, 1H), 4.90 (br, 1H), 2.99 (m, 2H), 2.71-2.48 (m, 8H), 2.21 (s,3H), 2.20 (m, 2H), 1.93 (m, 2H), 1.64 (m, 4H).

Compound 65, 4-[[3-(3,4-Dichlorophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 478 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-*d6*) δ9.23 (br, 1H), 8.95 (br, 1H), 7.82 (br, 1H), 7.69 (br, 1H),

7.45 (d, J = 8.8 Hz, 1H), 7.29-7.18 (m, 4H), 6.38 (br, 1H), 4.91 (br, 1H), 3.00 (m, 2H), 2.74-2.65 (m, 8H), 2.18 (m, 2H), 1.94 (m, 2H), 1.65 (m, 4H).

Compound 171, 4-[[3-(4-Chlorophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 444 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.99 (s, 1H), 8.31 (s, 1H), 7.66 (m, 1H), 7.46 (m, 4H), 7.24 (m, 3H), 6.21 (br, 1H), 4.87 (m, 1H), 3.00 (m, 2H), 2.72-2.49 (m, 8H), 2.18 (m, 2H), 1.93 (m, 2H), 1.65 (m, 4H).

Compound 173, 4-[[3-(4-Bromophenylureido)propyl](1-indanyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 476 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ7.63 (m, 1H), 7.39 (m, 2H), 7.34 (m, 4H), 7.27 (m, 1H), 5.25 (dd, J = 8.5, 3.4 Hz, 1H), 3.30 (m, 2H), 3.19 (m, 6H), 3.03 (m, 2H), 2.53 (m, 1H), 2.41 (m, 3H), 2.03 (m, 2H).

Compound 179, 4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-indanyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 476 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ7.63 (d, J = 7.8 Hz, 1H), 7.38 (m, 3H), 7.33 (m, 3H), 7.27 (m, 1H), 5.24 (dd, J = 8.6, 3.7 Hz, 1H), 3.29 (m, 4H), 3.18 (m, 4H), 3.02 (m, 2H), 2.53 (m, 1H), 2.41 (m, 3H), 2.02 (m, 2H).

Compound 181, 4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1,2,3,4-tetrahydro-1-naphthyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 490 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ7.64 (m, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.29 (m, 2H), 7.20 (m, 1H), 5.06 (m, 1H), 3.24 (m, 6H), 2.91-2.76 (m, 4H), 2.33 (m, 4H), 2.02 (m, 4H).

Compound 227, 4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-(4-methoxyphenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 60 and contains the following characteristics: MS(ES$^+$) m/e 494 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.57 (s, 1H), 7.88 (br, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.27 (m, 1H), 6.90 (m, 4H), 4.24 (q, J = 6.8 Hz, 1H),

3.75 (s, 3H), 3.26 (m, 2H), 3.13 (m, 1H), 2.98 (m, 1H), 2.91 (m, 2H), 2.43 (m, 2H), 1.90 (m, 3H), 1.81 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H).

Compounds 66-90, 175, 177, 183, 186, 188, 190, 195, 199, 201, 207, 209, 211, 214, 223, 226 can be obtained in an analogous manner to that of Compound 60.

Example 5. Synthesis of [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl]-diethylammonium iodide (Compound 91).

The following synthesis is depicted in Scheme 5.

A solution of N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound 1, 13.7 mg, 0.0381 mmol) in ethyl iodide (2 ml) was refluxed for 3 h, and concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and the plate was developed with 17% methanol/chloroform to afford [3-(phenylureido)propyl][2-(4-chlorophenyl)ethyl]diethylammonium iodide (15.4 mg, 78%): MS(ES$^+$) m/e 388 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.16 (m, 6H), 6.90 (m, 1H), 6.54 (m, 1H), 3.50 (m, 2H), 3.33 (m, 6H), 3.25 (m, 2H), 2.96 (m, 2H), 1.91 (m, 2H), 1.28 (t, J = 7.1 Hz, 6H).

Compound 92, [3-(4-Bromophenylureido)propyl][2-(4-chlorophenyl)ethyl]-diethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES$^+$) m/e 466 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (br, 1H), 7.30 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 6.67 (t, J = 6.0 Hz, 1H), 3.60 (m, 2H), 3.32 (m, 6H), 3.24 (m, 2H), 2.98 (m, 2H), 1.91 (m, 2H), 1.30 (t, J = 7.2 Hz, 6H).

Compound 298, [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](4-chlorobenzyl)ethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES$^+$) m/e 484 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.40 (m, 4H), 7.34 (d, J = 8.5 Hz, 2H), 7.11 (m, 6H), 6.87 (t, J = 7.3 Hz, 1H), 6.73 (t, J = 6.1 Hz, 1H), 4.65 (d, J = 13.4 Hz, 1H), 4.57 (d, J = 13.4 Hz, 1H), 3.78 (m, 1H), 3.66 (m, 1H), 3.39 (m, 1H), 3.29 (m, 2H), 3.19 (m, 4H), 3.11 (m, 1H), 2.00 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H).

Compound 302, [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](benzyl)ethylammonium iodide, can be obtained in an analogous manner

to that described for compound 91 and contains the following characteristics: MS(ES^+) m/e 450 $[M-I]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.60 (m, 2H), 7.51 (m, 3H), 7.33 (m, 6H), 7.26 (m, 2H), 7.00 (m, 1H), 4.63 (s, 2H), 3.48-3.30 (m, 8H), 3.18 (m, 2H), 2.17 (m, 2H), 1.51 (t, J = 7.1 Hz, 3H).

Compound 309, [3-(Phenylureido)propyl][2-(3-chlorophenyl)ethyl]diethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES^+) m/e 388 $[M-I]^+$; ^1H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 8.09 (s, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.13 (m, 5H), 7.08 (d, J = 7.3 Hz, 1H), 6.88 (t, J = 7.3 Hz, 1H), 6.69 (m, 1H), 3.65 (m, 2H), 3.35 (m, 6H), 3.24 (m, 2H), 3.00 (m, 2H), 1.93 (m, 2H), 1.32 (t, J = 7.1 Hz, 6H).

Compound 320, [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(methoxycarbonyl)butyl] ethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES^+) m/e 474 $[M-I]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.36 (m, 2H), 7.32 (m, 4H), 7.24 (m, 2H), 6.98 (m, 1H), 3.66 (s, 3H), 3.44 (m, 6H), 3.31 (m, 4H), 3.05 (m, 2H), 2.44 (m, 2H), 1.98 (m, 2H), 1.78 (m, 2H), 1.67 (m, 2H), 1.36 (m, 3H).

Compound 323, [5-(Phenylureido)pentyl][2-(4-chlorophenyl)ethyl]diethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES^+) m/e 416 $[M-I]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (bs, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.24 (m, 4H), 7.16 (m, 2H), 6.89 (t, J = 7.3 Hz, 1H), 6.40 (m, 1H), 3.43-3.28 (m, 10H), 3.01 (m, 2H), 1.78 (m, 2H), 1.58 (m, 4H), 1.29 (t, J = 7.3 Hz, 6H).

Compound 343, [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](2-chlorobenzyl)ethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES^+) m/e 484 $[M-I]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.71 (dd, J = 7.6, 1.5 Hz, 1H), 7.48 (m, 4H), 7.40 (m, 1H), 7.22 (m, 2H), 7.18 (m, 4H), 7.09 (m, 1H), 6.93 (m, 1H), 4.80 (d, J = 2.2 Hz, 2H), 3.98 (m, 2H), 3.57-3.48 (m, 6H), 3.12 (m, 2H), 2.13 (m, 2H), 1.49 (t, J = 7.1 Hz, 3H).

Compound 351, [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](2,5-difluorobenzyl)ethylammonium iodide, can be obtained in an analogous manner to that

described for compound 91 and contains the following characteristics: MS(ES$^+$) m/e 486 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (bs, 1H), 7.43 (m, 3H), 7.18-7.10 (m, 7H), 6.92-6.84 (m, 3H), 4.75 (d, J = 13.9 Hz, 1H), 4.69 (d, J = 13.9 Hz, 1H), 3.85 (m, 2H), 3.47-3.26 (m, 6H), 3.18 (m, 2H), 2.11 (m, 2H), 1.47 (t, J = 7.1 Hz, 3H).

Compound 352, [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](3-fluorobenzyl)ethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES$^+$) m/e 470 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.42 (m, 4H), 7.34 (d, J = 7.8 Hz, 1H), 7.23 (m, 1H), 7.17 (m, 6H), 6.91 (m, 1H), 6.77 (m, 1H), 4.73 (d, J = 13.7 Hz, 1H), 4.67 (d, J = 13.7 Hz, 1H), 3.74 (m, 2H), 3.45-3.11 (m, 8H), 2.08 (m, 2H), 1.45 (t, J = 6.8 Hz, 3H).

Compound 394, [3-(4-Cyanophenylureido)propyl][2-(3-chlorophenyl)ethyl][2-(2-methoxyehtoxy)ethyl] ethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES$^+$) m/e 487 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (bs, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 9.1 Hz, 2H), 7.13 (m, 3H), 7.06 (m, 1H), 6.96 (t, J = 6.1 Hz, 1H), 3.91 (m, 2H), 3.77 (dd, J = 11.2, 5.9 Hz, 2H), 3.66-3.35 (m, 12H), 3.23 (s, 3H), 3.07 (t, J = 8.8 Hz, 2H), 1.92 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H).

Compound 438, [3-(4-Methoxyphenylureido)propyl][2-(3-chlorophenyl)ethyl][2-(2-methoxyehtoxy)ethyl] ethylammonium iodide, can be obtained in an analogous manner to that described for compound 91 and contains the following characteristics: MS(ES$^+$) m/e 492 [M-I]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br, 1H), 7.30 (d, J = 9.0 Hz, 2H), 7.14 (m, 3H), 7.09 (m, 1H), 6.68 (m, 3H), 3.89 (m, 2H), 3.76 (m, 2H), 3.66 (s, 3H), 3.59 (m, 4H), 3.46-3.37 (m, 8H), 3.23 (s, 3H), 3.03 (m, 2H), 1.91 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H).

Compounds 294, 295, 297, 299-301, 303-308, 310-314, 317-319, 321, 324-342, 344-350, 353-393, 395-437, 439-453 can be obtained in an analogous manner to that of Compound 91.

Example 6. Synthesis of Active Compounds by Solid Phase Synthesis

The following synthesis is depicted in Scheme 6.

Step 1: ***Reductive amination of the linker to the resin.*** Novabiochem 2-(4-formyl-3-methoxy)phenoxyethyl polystyrene resin (0.5 mmol/g, 100g, 50 mmol) was added to a 500 ml erlenmyer flask. 3-Chloropropylamine hydrochloride (35.03g, 0.3 mole), 100 ml of 1% HOAc in DMF, and DIEA (53 ml, 0.3 mole) were added to the flask. The reaction mixture was stirred for one hour, $NaBH(OAc)_3$ (0.3 mole) was added and the reaction was stirred for four hours.

The reaction mixture was poured into a 1000 ml sintered glass funnel and the solvent was removed by vacuum. DMF (500 ml) was added and the solution was mixed thoroughly for five minutes. A vacuum again removed the solvent. This wash process was repeated two times. The resin was then washed in this manner three times with MeOH, three times with DCM, and three times with MeOH. The final resin was dried under a vacuum until constant weight.

Step 2: ***Protection of linker.*** The resin prepared above (30g, 15mmole) was placed into a 250 ml roundbottom flask. To this flask, DCM was added until a thick slurry was obtained. DIEA (31.3 ml, 90 mmole) was added followed by the p-nitrobenzylchloroformate, which was added in 5g batches as a solid (19.4g, 45 mmole) while being stirred magnetically. The reaction was stirred for two hours. The reaction mixture was poured into a 1 L sintered glass funnel and a vacuum removed the solvent. The resin was resuspended in DCM and mixed thoroughly for five minutes before the solvent was again removed. This was repeated two more times with DCM, and three times with MeOH. The resin was dried under a vacuum until constant weight.

Step 3: ***Displacement of chlorine by amine.*** The protected resin prepared above was transferred to a 96 well polyfiltronics plate (80mg, 0.04 mmole per well). The plate was placed onto a vacuum block and the resin was washed into their wells with DMSO. The solvent was removed by vacuum. The plate was transferred onto a clamp and the bottom was sealed. To each of the wells with resin, a solution of TBAI (300 µl, 0.16 M) in DMSO and amine (R1-NH2, 0.26 mmole) were added. The plate was sealed from the top and placed into an oven at 80 °C for 48 hours.

The plate was unclamped and placed onto the vacuum block where the solvent was removed by vacuum. The plate was placed over a catch tray and each well with resin received roughly 1.5ml of DMSO each with a squirt bottle. The solvent was allowed to drain by gravity, then the remaining solvent was removed by vacuum. This was repeated

two more times with DMSO, three times with MeOH, three times with DCM, and three more times with MeOH. The plate was dried under a vacuum.

Step 4: ***Reductive amination of secondary amine.*** The plate was placed onto the vacuum block and the resin was washed down with a solution of 30% EtOH in DMF. The solvent was removed with a vacuum. The plate bottom was sealed with the clamp and the 30% EtOH in DMF (300µl) was added to each well with resin. Aldehydes (R2-CHO, 0.2 mmole) were added to their respective wells. The plate was sealed from the top and shaken for 2 hours. The plate was unclamped from the top and BAP (0.2 mmole) was added to each of the wells with resin. The plate was then reclamped and shaken for 48 hours. The plate was unclamped and a vacuum removed the solvent. Each well was washed three times with DMF, three times MeOH, and three times DCM.

Step 5: ***Deprotection of the p-nitrobenzyl carbamate.*** A solution of $SnCl_2$ dihydrate in DMF (2.0 M) was prepared. The plate was again clamped and to each of the wells with resin, this solution was added (0.5 ml). The top of the plate was sealed and was allowed to stand overnight. The plate was unclamped, and washed two times with DMF. This deprotection was repeated a second time. The final wash solvents were three times DMF, three times MeOH, three times DMF, two times MeOH, then three times DCM.

Step 6: ***Acylation of linker.*** To the deprotected plate, a solution of DIEA in THF (150 ul, 1.2 M) was added to all wells containing resin. These wells each received the respective isocyanates (R3-NCO, 0.09 mmole) in THF (150 µl). The plate was sealed and allowed to stand for three hours. The plate was unclamped and washed with the following solvents: three times DCM, three times MeOH, three times DMF, three times MeOH, then three times DCM. The plate was dried under a vacuum.

Step 7: ***Isolation of Final Products.*** The dried plate was placed into the HCl gas cleavage apparatus. The system was flushed with nitrogen for ten minutes followed by a 10 minute flush with HCl gas. The system was sealed and the plate was allowed to sit for one hour in HCl gas. The system was recharged after the hour and the plate was allowed to sit for an additional hour. The system was flushed with nitrogen for ten minutes and the plate was removed. The plate was placed on a tarred 2 ml deepwell plate and the resin treated with a DCM wash (300µl). The solvent was allowed to drain by gravity and was followed by a MeOH wash (300µl). The process was repeated with a DCM and two MeOH washes. The collected filtrate was left out to dry overnight. The final material was placed into a

desicator and was dried under a vacuum. The dried plate was weighed and the yield calculated; each well had an average weight of 12 mg.

Example 7 Synthesis of N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl 2-hydroxy-1,3-diaminopropane (Compound 163)

The following synthesis is depicted in Scheme 7.

Step1: To a suspension of potassium phthalimide (5.0 g, 27 mmol) in DMF (75 ml) was added epibromohydrin (2.5 ml, 29 mmol), and the mixture was stirred at 120 °C for 3 h. After adding water, the mixture was extracted with (hexane/ethyl acetate = 3/1), washed with brine, dried over magnesium sulfate, and then filtered. Concentrating under vacuum gave N-(2,3-epoxypropyl)phthalimide (2.81 g, 51%) which was used in the next step without further purification.

Step2: To a mixture of 2-(4-chlorophenyl)ethylamine (3.00 g, 19.3 mmol) and acetaldehyde (1.40 ml, 25.0 mmol) in MeOH (30 ml) were added $NaBH_3CN$ (1.33 g, 21.2 mmol) and HOAc (1.22 ml, 21.3 mmol), and the mixture was stirred at RT for 24 h. After adding saturated $NaHCO_3$ and water, the mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was dissolved in *o*-dichlorobenzene (40 ml). To the solution was added N-(2,3-epoxypropyl)phthalimide (2.81 g), and the solution was stirred at 140 °C for 3 h. The reaction mixture was chromatographed on silica gel (eluting with 1% methanol/chloroform) to afford N-[3-[[2-(4-chlorophenyl)ethyl](ethyl)amino]-2-hydroxypropyl]phthalimide (2.30 g, 31%): MS(ES^+) m/e 387 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.86 (dd, J = 5.4, 3.2 Hz, 2H), 7.73 (dd, J = 5.4, 2.9 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.96 (m, 2H), 3.81 (dd, J = 13.9, 6.8 Hz, 1H), 3.70 (dd, J = 13.9, 4.6 Hz, 1H), 2.90-2.60 (m, 8H), 1.09 (br, 3H).

Step3: To a solution of N-[3-[[2-(4-chlorophenyl)ethyl](ethyl)amino]-2-hydroxypropyl]phthalimide (2.27 g, 5.88 mmol) in EtOH (50 ml) was added hydrazine monohydrate (1.15 ml, 23.7 mmol), and the mixture was stirred at RT for 5 h. After adding 1N-HCl, the mixture was washed with chloroform, neutralized with 1N-NaOH, and then washed with chloroform. After adding 1N-NaOH (pH = 12), the mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was dissolved in

CH_2Cl_2 (30 ml). To the solution was added phenyl isocyanate (0.35 ml, 3.2 mmol), and the solution was stirred at RT for 3 h. The reaction mixture was chromatographed on silica gel (eluting with 2% methanol/chloroform to 10% methanol/chloroform) to afford N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-2-hydroxy-1,3-diaminopropane (828 mg, 38%): MS(ES^+) m/e 376 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.31 (m, 5H), 7.24 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.05 (m, 2H), 5.44 (br, 1H), 3.73 (m, 1H), 3.47 (m, 1H), 3.12 (dt, J = 14.1, 5.9 Hz, 1H), 2.85-2.45 (m, 8H), 1.05 (t, J = 7.1 Hz, 3H).

Example 8. Synthesis of 4-[[3-(4-chlorophenylthioureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 164)

The following synthesis is depicted in Scheme 8.

Step1: To a solution of methyl 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (39 mg, 0.09 mmol) in EtOH (1 ml) was added hydrazine monohydrate (23 µl, 0.45 mmol), and the mixture was stirred at RT for 3.5 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. To the filtrate was added 4-chlorophenyl isothiocyanate (17 mg, 0.1 mmol), and the mixture was stirred at RT for 30 min. The residue was adsorbed on a plate of silica gel and then developed with 3% methanol/chloroform to afford methyl 4-[[3-(4-chlorophenylthioureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (25 mg, 29%): MS(ES^+) m/e 474 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (br, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.32 (m, 2H), 7.12-7.01 (m, 5H), 6.14 (br, 1H), 3.93 (m, 1H), 3.68 (m, 1H), 3.64 (s, 3H), 3.63 (m, 1H), 2.71 (m, 2H), 2.50-2.25 (m, 6H), 1.96 (m, 2H), 1.79-1.53 (m, 6H).

Step2: To a solution of methyl 4-[[3-(4-chlorophenylthioureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (25 mg, 0.052 mmol) in 10% water/methanol (4.4 ml) was added lithium hydroxide monohydrate (7.5 mg, 0.18 mmol), and the mixture was stirred at RT for 24 h. The reaction mixture was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 3% methanol/chloroform to afford 4-[[3-(4-chlorophenylthioureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (21 mg, 90%): MS(ES^+) m/e 460 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 10.60 (br, 1H), 9.29 (br, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 7.6

Hz, 1H), 7.24 (m, 3H), 7.15 (m, 3H), 4.74 (t, J = 7.6 Hz, 1H), 3.82 (m, 1H), 3.69 (m, 1H), 3.26 (m, 1H), 3.12 (m, 1H), 2.90 (m, 2H), 2.77 (m, 2H), 2.53 (dd, J = 15.6, 7.3 Hz, 1H), 2.26 (m, 2H), 2.15 (m, 1H), 1.99 (m, 2H), 1.83 (m, 2H), 1.71 (m, 2H).

Compound 288, 4-[[3-(4-Bromophenylthioureido)propyl][(1*R*)-1-indanyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 164 and contains the following characteristics: MS(ES$^+$) m/e 490 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (bs, 1H), 9.25 (bs, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.30 (m, 3H), 7.16 (m, 1H), 4.95 (m, 1H), 3.81 (m, 1H), 3.67 (m, 1H), 3.12-2.94 (m, 4H), 2.87 (m, 2H), 2.59 (dd, J = 16.3, 7.3 Hz, 1H), 2.41 (m, 1H), 2.19 (m, 3H), 2.01 (m, 2H), 1.77 (m, 1H).

Compound 290, 4-[[3-(4-Bromophenylthioureido)propyl][(1*R*)-1,2,3,4-tetrahydro-1-naphthyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 164 and contains the following characteristics: MS(ES$^+$) m/e 504 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (br, 1H), 9.21 (br, 1H), 7.59 (m, 3H), 7.40 (m, 2H), 7.23 (m, 2H), 7.17 (m, 2H), 4.74 (m, 1H), 3.82 (m, 1H), 3.67 (m, 1H), 3.26 (m, 1H), 3.11 (m, 1H), 2.90 (m, 2H), 2.79 (m, 2H), 2.53 (m, 1H), 2.26 (m, 3H), 2.00 (m, 3H), 1.86-1.72 (m, 3H).

Compounds 246-257, 289 can be obtained in an analogous manner to that of Compound 164.

Example 9. Synthesis of 4-[[(3*S*)-3-(4-bromophenylureido)-3-(*tert*-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 165 and 166)

The following synthesis is depicted in Scheme 9.

Step 1: To a mixture of Fmoc-L-Asp(OtBu)-OH (100 mg, 0.243 mmol) and 1,2,3,4-tetrahydro-1-naphthylamine (39 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) were added WSC.HCl (51 mg, 0.27 mmol), HOBt.H_2O (36 mg, 0.27 mmol) and triethylamine (34 µl, 0.27 mmol), and the mixture was stirred at RT for 5 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 2.5% methanol/chloroform to afford *tert*-butyl (2*S*)-2-[[(9*H*-9-fluorenylmethoxy)carbonyl]amino]-4-oxo-4-(1,2,3,4-tetrahydro-1-

naphthylamino)butanoate (113 mg, 86%): MS(ES^+) m/e 541 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 7.3 Hz, 2H), 7.33 (m, 2H), 7.24 (m, 2H), 7.16-6.97 (m, 4H), 6.05 (dd, J = 20.0, 7.8 Hz, 1H), 5.74 (m, 1H), 5.10 (br, 1H), 4.42 (m, 1H), 4.31 (m, 1H), 4.24 (m, 1H), 4.16 (m, 1H), 2.87-2.65 (m, 4H), 1.96 (m, 1H), 1.74 (m, 3H), 1.43 (s, 9H).

Step 2: To a solution of *tert*-butyl (2*S*)-2-[[(9*H*-9-fluorenylmethoxy)carbonyl]amino]-4-oxo-4-(1,2,3,4-tetrahydro-1-naphthylamino)butanoate (43 mg,0.080 mmol) in THF (2 ml) was added BH_3-SMe_2 (0.20 ml, 0.40 mmol), and the mixture was stirred at RT for 15 h. After adding 1N-HCl (1 ml), the mixture was stirred at RT for 1.5 h, and then 1N-NaOH (1 ml) was added. The mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 6% methanol/chloroform to afford *tert*-butyl (2*S*)-2-[[(9*H*-9-fluorenylmethoxy)carbonyl]amino]-4-(1,2,3,4-tetrahydro-1-naphthylamino)butanoate (23 mg, 54%): MS(ES^+) m/e 527 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.6, 3.9 Hz, 2H), 7.52 (d, J = 7.3 Hz, 2H), 7.32 (m, 3H), 7.22 (m, 2H), 7.04 (m, 3H), 6.69 (br, 1H), 6.52 (br, 1H), 4.35-4.10 (m, 4H), 3.70 (m, 1H), 2.86-2.61 (m, 4H), 1.90-1.60 (m, 6H), 1.38 (s, 9H).

Step 3: To a solution of *tert*-butyl (2*S*)-2-[[(9*H*-9-fluorenylmethoxy)carbonyl]amino]-4-(1,2,3,4-tetrahydro-1-naphthylamino)butanoate (16 mg,0.030 mmol) in MeOH (0.5 ml) were added succinic semialdehyde (15 wt.% solution in water, 48 µl, 0.077 mmol), HOAc (2 µl, 0.035 mmol) and $NaBH_3CN$ (2.3 mg, 0.074 mmol), and the mixture was stirred at RT for 6 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 4-[[(3S)-3-(tert-butoxycarbonyl)-3-[[(9*H*-9-fluorenylmethoxy)carbonyl]amino]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (18 mg, 98%): MS(ES^+) m/e 613 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (br, 1H), 7.76 (d, J = 7.3 Hz, 2H), 7.61 (m, 3H), 7.40 (t, J = 7.3 Hz, 2H), 7.31 (m, 2H), 7.15 (m, 2H), 7.06 (d, J = 7.6 Hz, 1H), 5.64 (br, 1H), 4.36 (m, 2H), 4.22 (m, 3H), 2.75-2.17 (m, 8H), 2.10-1.65 (m, 8H), 1.42 (s, 9H).

Step 4: To a solution of 4-[[(3S)-3-(tert-butoxycarbonyl)-3-[[(9*H*-9-fluorenylmethoxy)carbonyl]amino]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (18 mg, 0.029 mmol) in DMF (0.4 ml) was added piperidine (0.1 ml), and the mixture was stirred at RT for 1.5 h. The reaction mixture was concentrated under vacuum to dryness, and the residue was dissolved in CH_2Cl_2 (0.5 ml). To the solution was added 4-bromophenyl isocyanate (8.7 mg, 0.044 mmol), and the mixture was stirred at RT for 2h. The reaction mixture was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 2 diastereoisomers of 4-[[(3S)-3-(4-bromophenylureido)-3-(tert-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (6.8 mg, 39%, less polar isomer, Compound 165) : MS(ES^+) m/e 588 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (br, 1H), 8.38 (br, 1H), 7.99 (br, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.08 (m, 3H), 4.81 (t, J = 7.3 Hz, 1H), 4.41 (m, 1H), 3.42 (m, 1H), 2.97 (m, 1H), 2.71 (m, 1H), 2.59 (m, 1H), 2.46 (dd, J = 16.3, 7.1 Hz, 1H), 2.18 (m, 2H), 1.95-1.74 (m, 4H), 1.62 (m, 1H), 1.48 (m, 1H), 1.32 (s, 9H).

(7.4 mg, 43%, more polar isomer, Compound 166): MS(ES^+) m/e 588 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (br, 1H), 8.57 (br, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.42 (br, 1H), 7.33 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.15 (m, 2H), 7.07 (m, 1H), 4.57 (t, J = 7.3 Hz, 1H), 4.26 (m, 1H), 3.25 (m, 1H), 2.92 (m, 1H), 2.69 (m, 5H), 2.40 (m, 1H), 2.11 (m, 4H), 1.90 (m, 2H), 1.65 (m, 2H), 1.33 (s, 9H).

The absolute configuration at the chiral carbon of 1,2,3,4-tetrahydro-1-naphthyl is not determined.

Example 10. Synthesis of 4-[[3-(4-bromophenylureido)-2-hydroxypropyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 167)

The following synthesis is depicted in Scheme 10.

Step 1: To a solution of 1,2,3,4-tetrahydro-1-naphthylamine (99 mg, 0.68 mmol) in *o*-dichlorobenzene (1 ml) was added N-(2,3-epoxypropyl)phthalimide (137 mg, 0.68 mmol), and the mixture was stirred at 150 °C for 4 h. The reaction mixture was chromatographed on silica gel (eluting with 0.5% methanol/chloroform) to afford N-[2-hydroxy-3-(1,2,3,4-tetrahydro-1-naphthylamino)propyl]phthalimide (108 mg, 47%): MS(ES^+) m/e 351 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.66 (m, 2H),

7.36 (m, 1H), 7.10 (m, 2H), 7.02 (m, 1H), 6.77 (br, 1H), 5.09 (m, 1H), 3.98 (m, 1H), 3.86-3.63 (m, 3H), 2.95-2.60 (m, 4H), 1.91-1.66 (m, 4H).

Step 2: To a solution of N-[2-hydroxy-3-(1,2,3,4-tetrahydro-1-naphthylamino)propyl]phthalimide (93 mg, 0.27 mmol) in MeOH (1 ml) were added succinic semialdehyde (15 wt.% solution in water, 220 µl, 0.35 mmol), HOAc (17 µl, 0.30 mmol) and $NaBH_3CN$ (18 mg, 0.29 mmol), and the mixture was stirred at RT for 2.5 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 4-[[2-hydroxy-(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (101 mg, 87%): MS(ES^+) m/e 437 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (br, 1H), 7.80 (m, 2H), 7.73-7.52 (m, 3H), 7.11 (t, J = 7.3 Hz, 1H), 7.02 (m, 1H), 6.92-6.78 (m, 1H), 4.63 (br, 1H), 4.44-3.96 (m, 2H), 3.77-3.54 (m, 2H), 2.99-2.81 (m, 1H), 2.77-2.51 (m, 5H), 2.43 (m, 1H), 2.32 (m, 1H), 2.19-2.04 (m, 1H), 1.97 (m, 1H), 1.83 (m, 2H), 1.66 (m, 2H).

Step 3: To a solution of 4-[[2-hydroxy-(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (68 mg, 0.16 mmol) in EtOH (1 ml) was added hydrazine monohydrate (38 µl, 0.78 mmol), and the mixture was stirred at RT for 3 h. The reaction mixture was concentrated under vacuum to dryness, and the residue was suspended in CH_2Cl_2 (2 ml). To the suspension was added 4-bromophenyl isocyanate (47 mg, 0.24 mmol), and the mixture was stirred at RT for 40 h. The reaction mixture was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 4-[[3-(4-bromophenylureido)-2-hydroxypropyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (13 mg, 16%): MS(ES^+) m/e 504 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d6*) δ 8.74 (s, 1H), 8.07 (br, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.36 (m, 4H), 7.13-7.00 (m, 3H), 6.15 (m, 1H), 3.92 (m, 1H), 3.66-3.45 (m, 3H), 2.70 (m, 1H), 2.67 (m, 2H), 2.51 (m, 2H), 2.36 (m, 2H), 2.25 (m, 1H), 2.14 (m, 1H), 2.02 (m, 1H), 1.19 (m, 1H), 1.67-1.49 (m, 3H).

Example 11. Synthesis of 4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanamide (Compound 193)

The following synthesis is depicted in Scheme 11.

To a solution of methyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (40 mg, 0.080 mmol) and formamide (11 mg, 0.24 mmol) in DMF (2 ml) was added sodium methoxide (0.5 M solution in MeOH, 112 µl, 0.056 mmol), and the mixture was stirred at 100 °C for 2.5 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanamide (17 mg, 43%): MS(ES$^+$) m/e 487 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.00 (br, 1H), 7.82 (br, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.31 (s, 4H), 7.12 (m, 2H), 7.05 (m, 1H), 6.08 (br, 1H), 5.64 (br, 1H), 3.99 (m, 1H), 3.41 (m, 1H), 3.22 (m, 1H), 2.70 (m, 1H), 2.61 (m, 1H), 2.55 (m, 1H), 2.39 (m, 3H), 2.12 (m, 2H), 1.96 (m, 3H), 1.87 (m, 1H), 1.64 (m, 4H).

Example 12. Synthesis of 3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[(phenylsulfonyl)carbamoyl]propane (Compound 196)

The following synthesis is depicted in Scheme 12.

To a mixture of 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (20 mg, 0.041 mmol) and benzenesulfonamide (7.0 mg, 0.045 mmol) in CH_2Cl_2 (1 ml) were added WSC.HCl (8.6 mg, 0.045 mmol) and DMAP (5.5 mg, 0.045 mmol), and the mixture was stirred at RT for 18 h. The reaction mixture was purified by preparative normal phase HPLC using linear gradients of (A) chloroform and (B) methanol (2-4% B, in 0-2 min; 4-5% B, in 2-6 min; 5% B, in 6-12 min) at a flow rate of 12 ml/min. Fractions containing the major peak were pooled and concentrated to afford 3-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[(phenylsulfonyl)carbamoyl]propane (5.4 mg, 21%): MS(ES$^+$) m/e 627 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.27 (s, 1H), 8.05 (m, 2H), 7.50 (m, 3H), 7.44 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 7.23 (m, 3H), 7.15 (d, J = 7.0 Hz, 1H), 7.02 (m, 1H), 6.92 (m, 1H), 4.72 (m, 1H), 3.73 (m, 1H), 3.58 (m, 1H), 3.21 (m, 1H), 2.96 (m, 1H), 2.79-2.65 (m, 5H), 2.57 (m, 1H), 2.17 (m, 1H), 2.03 (m, 1H), 1.94-1.66 (m, 4H).

Compounds 197, 210 can be obtained in an analogous manner to that of Compound 196.

Example 13. Synthesis of 4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-butanol (Compound 203)

The following synthesis is depicted in Scheme 13.

Lithium hydroxide monohydrate (11 mg, 0.26 mmol) was added to a solution of 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butyl acetate (67 mg, 0.13 mmol) in 10% water/methanol (1.1 ml). After stirring at RT for 16 h, additional lithium hydroxide monohydrete (22 mg, 0.52 mmol) was added. The reaction mixture was stirred at RT for 17 h, and then concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-butanol (48 mg, 77%): MS(ES$^+$) m/e 476 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-*d6*) δ8.52 (br, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.36 (m, 4H), 7.11-7.03 (m, 3H), 6.10 (br, 1H), 4.33 (br, 1H), 3.90 (m, 1H), 3.37 (m, 2H), 3.13 (m, 1H), 3.02 (m, 1H), 2.67 (m, 2H), 2.54-2.47 (m, 4H), 1.93 (m, 2H), 1.58 (m, 4H), 1.44 (m, 4H).

Compounds 205, 216 can be obtained in an analogous manner to that of Compound 203.

Example 14. Synthesis of 3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-(1*H*-tetrazol-5-yl)propane (Compound 218)

The following synthesis is depicted in Scheme 14.

Step 1: To a mixture of N-[3-(1,2,3,4-tetrahydro-1-naphthylamino)propyl]phthalimide (569 mg, 1.7 mmol), potassium carbonate (709 mg, 5.1 mmol) and potassium iodide (280 mg, 1.7 mmol) in CH_3CN (20 ml) was added 4-bromobutyronitrile (754 mg, 5.1 mmol). The mixture was refluxed under stirring for 18 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 20% ethyl acetate/chloroform) to afford 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butyronitrile (336 mg, 50%): MS(ES$^+$) m/e 402 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.82 (dd, J = 5.4, 2.9 Hz, 2H), 7.70 (m, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.11 (m, 1H), 7.02 (m, 2H), 3.95 (m, 1H), 3.78 (m, 1H), 3.59 (m, 1H), 2.73 (m, 2H), 2.64 (m, 1H), 2.51 (m, 4H), 2.35 (m, 1H), 1.98 (m, 2H), 1.83 (m, 4H), 1.63 (m, 2H).

Step 2: To a solution of 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butyronitrile (336 mg, 0.84 mmol) in xylene (5 ml) was added trimethyltin azide (378 mg, 1.84 mmol). The mixture was stirrred at 115 °C for 18 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was dissolved with 17% THF/CH_2Cl_2 (2.4 ml). To the solution was added 10 N NaOH solution (107 µl, 1.07 mmol). After srirring at RT for 30 min, triphenylmethyl chloride (297 mg, 1.07 mmol) was added, and the mixture was stirred at RT for 7 h, After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave 3-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[1-(triphenylmethyl)tetrazol-5-yl]propane (125 mg, 22%) which was used in the next step without further purification.

Step 3: To a solution of 3-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[1-(triphenylmethyl)tetrazol-5-yl]propane (50 mg, 0.073 mmol) in EtOH (1 ml) was added hydrazine monohydrate (17 µl, 0.36 mmol), and the mixture was stirred at RT for 3 h. The reaction mixture was concentrated under vacuum, and then water was added. The mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. To the filtrate was added 4-bromophenyl isocyanate (17 mg, 0.088 mmol), and the mixture was stirred at RT for 1 h. The reaction mixture was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 3% methanol/chloroform to afford 3-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[1-(triphenylmethyl)tetrazol-5-yl]propane (Compound 217, 33 mg, 60%): MS(ES^+) m/e 756 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.62 (m, 1H), 7.53 (br, 1H), 7.34 (m, 10H), 7.09 (m, 12H), 5.79 (br, 1H), 4.05 (m, 1H), 3.48 (m, 1H), 3.31 (m, 1H), 3.17 (m, 1H), 2.74 (m, 4H), 2.55 (m, 1H), 2.44 (m, 2H), 1.96 (m, 3H), 1.86 (m, 1H), 1.72 (m, 2H), 1.61 (m, 2H).

Step 4: To a solution of 3-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[1-(triphenylmethyl)tetrazol-5-yl]propane (30 mg, 0.04 mmol) in THF (2 ml) was added 10 wt% HCl solution (1 ml), and the mixture was stirred at RT for 4 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. The filtrate was adsorbed on a plate of silica gel and then developed with 20% methanol/chloroform to afford 3-[[3-(4-

bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-(1*H*-tetrazol-5-yl)propane (12 mg, 57%): MS(ES$^+$) m/e 514 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (s, 1H), 7.64 (m, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.21 (m, 2H), 7.11 (m, 1H), 3.31 (m, 1H), 3.21 (t, J = 6.3 Hz, 2H), 3.14 (m, 1H), 3.08 (m, 3H), 2.94-2.72 (m, 4H), 2.24 (m, 1H), 2.17-2.01 (m, 3H), 1.98-1.80 (m, 3H), 1.71 (m, 1H).

Compounds 222 can be obtained in an analogous manner to that of Compound 218.

Example 15. Synthesis of Methyl 4-[[3-[4-(carboxy)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound 225)

The following synthesis is depicted in Scheme 15.

Lithium hydroxide monohydrate (2.5 mg, 0.060 mmol) was added to a solution of methyl 4-[[3-[4-(ethoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (28 mg, 0.057 mmol) in 7% water/methanol (4.3 ml). After stirring at RT for 24 h, additional lithium hydroxide monohydrete (5 mg, 0.12 mmol) was added. The reaction mixture was stirred at RT for 24 h, and then concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford methyl 4-[[3-[4-(carboxy)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (12 mg, 51%): MS(ES$^+$) m/e 468 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.85 (bs, 1H), 7.91 (m, 3H), 7.61 (m, 3H), 7.21 (m, 1H), 7.13 (m, 3H), 4.72 (m, 1H), 3.86 (s, 3H), 3.33 (m, 3H), 3.25 (m, 1H), 3.02 (m, 1H), 2.88 (m, 2H), 2.75 (m, 2H), 2.56 (m, 1H), 2.22 (m, 2H), 2.00 (m, 3H), 1.85 (m, 1H), 1.71 (m, 2H).

Compounds 235 can be obtained in an analogous manner to that of Compound 225 except for the use of compound 228 as starting material instead of methyl 4-[[3-[4-(ethoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate.

Example 16. Synthesis of 4-[[3-[4-(Ethoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 228)

The following synthesis is depicted in Scheme 16.

Step 1: To a solution of N-[3-(1,2,3,4-tetrahydro-1-naphthylamino)propyl]phthalimide (200 mg, 0.60 mmol) in MeOH (10 ml) were added succinic semialdehyde (15 wt.% solution in water, 0.45 ml, 0.72 mmol), HOAc (41 µl,

0.72 mmol) and $NaBH_3CN$ (45 mg, 0.72 mmol), and the mixture was stirred at RT for 2.5 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (207 mg, 82%): MS(ES^+) m/e 421 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.83 (dd, J = 5.6, 2.9 Hz, 2H), 7.72 (m, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.15 (m, 1H), 7.08 (m, 1H), 7.00 (d, J = 7.3 Hz, 1H), 4.28 (m, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 2.80-2.55 (m, 6H), 2.47 (m, 1H), 2.30 (m, 1H), 2.06-1.86 (m, 5H), 1.74-1.66 (m, 3H).

Step 2: To a solution of 4-[[(3-phthalimido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (137 mg, 0.32 mmol) in EtOH (5 ml) was added hydrazine monohydrate (63 µl, 1.3 mmol), and the mixture was stirred at RT for 4 h. The reaction mixture was concentrated under vacuum, and then water was added. The mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. To the filtrate was added 4-(ethoxycarbonyl)phenyl isocyanate (62 mg, 0.32 mmol), and the mixture was stirred at RT for 30 min. The reaction mixture was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 17% methanol/chloroform to afford 4-[[3-[4-(ethoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (25 mg, 16%): MS(ES^+) m/e 482 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ9.86 (s, 1H), 8.80 (br, 1H), 7.91 (m, 3H), 7.61 (m, 3H), 7.21 (m, 1H), 7.12 (m, 2H), 4.70 (t, J = 7.6 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.32 (m, 2H), 3.23 (m, 1H), 3.03-2.84 (m, 3H), 2.74 (m, 2H), 2.55 (m, 1H), 2.21 (m, 2H), 2.02-1.78 (m, 5H), 1.70 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H).

Compound 229, 4-[[3-(4-Iodophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 228 and contains the following characteristics: MS(ES^+) m/e 536 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ9.50 (bs, 1H), 7.70 (br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.22 (m, 1H), 7.14 (m, 3H), 4.69 (m, 1H), 3.30 (m, 2H), 3.22 (m, 1H), 2.99 (m, 1H), 2.87 (m, 2H), 2.75 (m, 2H), 2.53 (dd, J = 16.6, 7.3 Hz, 1H), 2.20 (m, 2H), 2.00-1.77 (m, 5H), 1.70 (m, 2H).

Compound 237, 4-[[3-[4-(Butoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 228 and contains the following characteristics: MS(ES$^+$) m/e 510 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.70 (br, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.72 (br, 1H), 7.62 (m, 3H), 7.20 (m, 3H), 7.13 (m, 1H), 4.71 (m, 1H), 4.27 (t, J = 6.6 Hz, 2H), 3.33 (m, 2H), 3.26 (m, 1H), 3.01 (m, 1H), 2.88 (m, 2H), 2.75 (m, 2H), 2.54 (m, 1H), 2.20 (m, 2H), 2.01 (m, 4H), 1.84 (m, 1H), 1.73 (m, 4H), 1.47 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H).

Compound 258, 4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-(4-bromophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 228 and contains the following characteristics: MS(ES$^+$) m/e 542 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.29 (bs, 1H), 7.82 (br, 1H), 7.69 (br, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 4.24 (m, 1H), 3.20 (m, 2H), 2.99 (m, 1H), 2.84 (m, 3H), 2.40 (m, 2H), 1.82 (m, 4H), 1.56 (d, J = 6.8 Hz, 3H).

Compound 269, 4-[[3-(4-Bromophenylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 228 and contains the following characteristics: MS(ES$^+$) m/e 482 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.47 (s, 1H), 7.68 (br, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.35 (m, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.05 (m, 2H), 6.92 (m, 1H), 4.30 (q, J = 6.8 Hz, 1H), 3.22 (m, 2H), 3.04 (m, 1H), 2.89 (m, 3H), 2.42 (m, 2H), 1.84 (m, 4H), 1.60 (d, J = 7.1 Hz, 3H).

Compound 272, 4-[[3-(4-Bromophenylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 228 and contains the following characteristics: MS(ES$^+$) m/e 498 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.38 (bs, 1H), 7.60 (br, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.31 (m, 6H), 7.20 (m, 1H), 4.26 (q, J = 7.1 Hz, 1H), 3.21 (m, 2H), 3.02 (m, 1H), 2.87 (m, 3H), 2.43 (m, 2H), 1.83 (m, 4H), 1.59 (d, J = 7.1 Hz, 3H).

Compound 293, 4-[[3-(4-Bromophenylureido)propyl][(1*S*)-1-(4-bromophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 228 and contains the following characteristics: MS(ES$^+$) m/e 542 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.37 (bs, 1H), 9.14 (br, 1H), 7.56 (br, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.23 (d, J =

8.5 Hz, 2H), 4.24 (m, 1H), 3.21 (m, 2H), 3.01 (m, 1H), 2.87 (m, 3H), 2.44 (m, 2H), 1.84 (m, 4H), 1.58 (d, J = 6.8 Hz, 3H).

Compounds 236, 259-268, 270, 271, 273, 277-279 can be obtained in an analogous manner to that of Compound 228.

Example 17. Synthesis of [3-(Phenylureido)propyl]bis[2-(4-chlorophenyl)ethyl]amine (Compound 238)

The following synthesis is depicted in Scheme 17.

Step 1: To a mixture of 4-chlorophenylacetic acid (500 mg, 3.0 mmol) and 2-(4-chlorophenyl)ethylamine (456 mg, 3.0 mmol) in DMF (50 ml) were added WSC.HCl (592 mg, 3.1 mmol), HOBt.H_2O (474 mg, 3.1 mmol) and triethylamine (0.43 ml, 3.1 mmol), and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, and filtered. Concentrating under vacuum gave N-[2-(4-chlorophenyl)ethyl]-(4-chlorophenyl)acetamide (819 mg, 89%) which was used in the next step without further purification.

Step 2: To a solution of N-[2-(4-chlorophenyl)ethyl]-(4-chlorophenyl)acetamide (100 mg, 0.33 mmol) in THF (2 ml) was added borane-methyl sulfide complex (2.0 M solution in THF, 1.6 ml, 3.2 mmol), and the mixture was stirred at 70 °C for 1.5 h. After adding 1 N HCl solution (4 ml), the mixture was stirred at RT for 1 h. After adding 5 wt% NaOH solution (4 ml), the mixture was extracted with chloroform, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 10% methanol/chloroform) to afford bis[2-(4-chlorophenyl)ethyl]amine (48 mg, 50%): MS(ES^+) m/e 294 $[M+H]^+$.

Step 3: To a mixture of bis[2-(4-chlorophenyl)ethyl]amine (48 mg, 0.16 mmol), potassium carbonate (44 mg, 0.32 mmol) and potassium iodide (26 mg, 0.16 mmol) in CH_3CN (2 ml) was added N-phenylcarbamoyl-3-bromopropylamine (215 mg, 0.64 mmol) in DMF (2 ml). The mixture was stirred at 80 °C for 18 h, and then concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford [3-(phenylureido)propyl]bis[2-(4-chlorophenyl)ethyl]amine (10 mg, 13%): MS(ES^+) m/e 470 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.24 (m, 9H), 7.03 (m, 5H), 6.59 (br, 1H), 3.24 (t, J = 6.3 Hz, 2H), 2.87 (m, 1H), 2.76 (m, 1H), 2.73-2.61 (m, 8H), 1.64 (m, 2H).

Example 18. Synthesis of 4-[[(3*S*)-3-(4-Bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 286)

The following synthesis is depicted in Scheme 18.

Step 1: To a mixture of 50% KOH (10 ml) and ether (10 ml) was added 1-methyl-3-nitro-1-nitrosoguamidine (1.0 g, 6.8 mmol) at 0 °C. After standing at 0 °C for 5 min, the organic layer was transferred to another erlenmeyer flask at 0 °C, and KOH pellets (1.0 g) were added. After standing at 0 °C for 5 min, the supernatant was added to a solution of 4-[[(3*S*)-3-(4-bromophenylureido)-3-(tert-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (Compound 166, 154 mg, 0.262 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(tert-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound 281, 128 mg, 81%): MS(ES$^+$) m/e 602 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.56 (m, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.20-7.04 (m, 5H), 6.62 (br, 1H), 5.61 (br, 1H), 4.41 (m, 1H), 4.03 (m, 1H), 3.63 (s, 3H), 2.73-2.25 (m, 8H), 2.10-1.81 (m, 6H), 1.64 (m, 2H), 1.43 (s, 9H).

Step 2: To a solution of methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(tert-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (121 mg, 0.202 mmol) in CH_2Cl_2 (5 ml) was added TFA (2 ml). After stirring at RT for 3 h, the reaction mixture was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford (2*S*)-2-(4-bromophenylureido)-4-[[3-(methoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (53 mg, 48%): MS(ES$^+$) m/e 546 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.77 (br, 1H), 7.82 (m, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.21 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 7.13 (br, 2H), 4.86 (m, 1H), 3.67 (s, 3H), 3.66 (m, 1H), 3.23-2.96 (m, 2H), 2.79 (m, 2H), 2.55 (m, 1H), 2.34 (m, 3H), 2.17 (m, 2H), 2.06 (m, 2H), 1.87 (m, 2H), 1.72 (m, 2H).

Step 3: To a mixture of (2*S*)-2-(4-bromophenylureido)-4-[[3-(methoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (25 mg, 0.046 mmol) and isopropylamine (6 µl, 0.055 mmol) in CH_2Cl_2 (1 ml) were added

WSC.HCl (10 mg, 0.052 mmol), HOBt.H_2O (7 mg, 0.052 mmol) and triethylamine (15 µl, 0.12 mmol), and the mixture was stirred at RT for 95 h. After adding water, the mixture was extracted with chloroform, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 5% methanol/chloroform to afford methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (Compound 282, 17 mg, 64%): MS(ES^+) m/e 587 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.60 (m, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.23-7.06 (m, 5H), 6.47 (br, 1H), 6.20 (br, 1H), 4.35 (m, 1H), 4.00 (m, 2H), 3.65 (s, 3H), 2.72-2.36 (m, 8H), 2.09-1.83 (m, 6H), 1.63 (m, 2H), 1.14 (t, J = 6.6 Hz, 6H).

Step 4: Lithium hydroxide monohydrate (10 mg, 0.24 mmol) was added to a solution of methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate (15 mg, 0.025 mmol) in 17% water/methanol (1.2 ml). After stirring at RT for 38 h, the reaction mixture was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford 4-[[(3*S*)-3-(4-bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid (17 mg, quant.): MS(ES^+) m/e 573 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ9.80 (bs, 1H), 8.16 (br, 1H), 7.68 (m, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.20 (m, 2H), 7.11 (m, 1H), 7.00 (d, J = 7.8 Hz, 1H), 4.62 (t, J = 7.8 Hz, 1H), 4.38 (m, 1H), 3.89 (m, 1H), 3.46 (m, 1H), 3.15 (m, 1H), 2.70 (m, 4H), 2.38 (m, 1H), 2.27 (m, 2H), 2.09 (m, 2H), 1.93 (m, 2H), 1.71 (m, 1H), 1.59 (m, 2H), 1.06 (m, 6H).

Compound 283, Methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(benzylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 282 except for the use of benzylamine instead of isopropylamine in step 3 and contains the following characteristics: MS(ES^+) m/e 635 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ7.56 (d, J = 6.1 Hz, 1H), 7.26 (m, 7H), 7.05 (m, 5H), 6.40 (br, 2H), 4.45 (m, 1H), 4.38 (m, 2H), 3.96 (m, 1H), 3.57 (s, 3H), 2.72-2.45 (m, 6H), 2.33 (m, 2H), 1.98-1.78 (m, 6H), 1. 59 (m, 2H).

Compound 287, 4-[[(3*S*)-3-(4-Bromophenylureido)-3-(benzylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be

obtained in an analogous manner to that described for compound 286 except for the use of benzylamine instead of isopropylamine in step 3 and contains the following characteristics: MS(ES$^+$) m/e 621 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.90 (bs, 1H), 8.34 (br, 1H), 7.65 (m, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.21-7.06 (m, 10H), 4.54 (m, 1H), 4.47 (m, 1H), 4.39 (dd, J = 15.1, 6.3 Hz, 1H), 4.21 (dd, J = 15.1, 5.4 Hz, 1H), 3.44 (m, 1H), 3.04 (m, 1H), 2.62 (m, 4H), 2.34 (m, 2H), 2.10 (m, 1H), 1.99 (m, 3H), 1.82 (m, 1H), 1.61-1.43 (m, 3H).

Compound 284, 4-[[(3*S*)-3-(4-Bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 286 except for the use of compound 165 as starting material instead of compound 166 and contains the following characteristics: MS(ES$^+$) m/e 573 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.77 (bs, 1H), 8.17 (br, 1H), 7.61 (d, J = 7.1 Hz, 1H), 7.40 (m, 2H), 7.26 (m, 2H), 7.12 (m, 2H), 7.06 (m, 1H), 6.83 (d, J = 7.8 Hz, 1H), 4.79 (t, J = 7.8 Hz, 1H), 4.29 (m, 1H), 3.84 (m, 1H), 3.35 (m, 1H), 2.99 (m, 1H), 2.64 (m, 4H), 2.51-2.41 (m, 2H), 2.30 (m, 1H), 2.13 (m, 1H), 1.89 (m, 3H), 1.68 (m, 1H), 1.52 (m, 1H), 1.37 (m, 1H), 1.05 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H).

Compound 285, 4-[[(3*S*)-3-(4-Bromophenylureido)-3-(benzylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 287 except for the use of compound 165 as starting material instead of compound 166 and contains the following characteristics: MS(ES$^+$) m/e 621 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.87 (bs, 1H), 8.36 (br, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.39 (m, 1H), 7.35 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 9.0 Hz, 2H), 7.15-6.98 (m, 8H), 4.63 (t, J = 7.8 Hz, 1H), 4.42 (m, 1H), 4.30 (dd, J = 14.9, 5.9 Hz, 1H), 4.20 (dd, J = 14.9, 5.6 Hz, 1H), 3.39 (m, 1H), 2.95 (m, 1H), 2.61 (m, 4H), 2.43 (m, 2H), 2.35 (m, 1H), 2.05 (m, 1H), 1.93-1.80 (m, 3H), 1.62 (m, 1H), 1.50 (m, 1H), 1.35 (m, 1H).

Example 19. Synthesis of [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl]bis(4-methylbenzyl)ammonium iodide (Compound 296)

The following synthesis is depicted in Scheme 19.

To a mixture of N-phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-1,3-diaminopropane (80 mg, 0.24 mmol) and potassium carbonate (100 mg, 0.72 mmol) in CH_3CN (2 ml) was added 4-methylbenzyl bromide (134 mg, 0.72 mmol). The mixture was refluxed under stirring for 1.5 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 33% methanol/chloroform to afford [3-(phenylureido)propyl][2-(4-chlorophenyl)ethyl]bis(4-methylbenzyl)ammonium iodide (101 mg, 68%): MS(ES^+) m/e 540 $[M-Br]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ8.13 (s, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 8.1 Hz, 4H), 7.19 (m, 8H), 7.07 (d, J = 8.5 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.86 (m, 1H), 4.81 (d, J = 13.2 Hz, 2H), 4.57 (d, J = 13.2 Hz, 2H), 3.75 (m, 2H), 3.35 (m, 2H), 3.25 (m, 2H), 3.19 (m, 2H), 2.11 (m, 2H), 1.60 (s, 6H).

Example 20. Synthesis of [3-(4-Bromophenylureido)propyl][(1*S*)-1-phenylethyl][3-(carboxy)propyl]ethylammonium trifluoroacetate (Compound 315)

The following synthesis is depicted in Scheme 20.

Lithium hydroxide monohydrate (10 mg, 0.24 mmol) was added to a solution of [3-(4-bromophenylureido)propyl][(1*S*)-1-phenylethyl][3-(methoxycarbonyl)propyl]ethylammonium iodide (24 mg, 0.05 mmol) in 10% water/methanol (3.3 ml). After stirring at RT for 4.5 h, the reaction mixture was concentrated under vacuum to dryness. The residue was purified by preparative reverse phase HPLC using linear gradients of (A) 0.05% TFA/H_2O and (B) 0.05% TFA/CH_3CN (20-80% B, in 0-15 min; 80% B, in 15-18 min) at a flow rate of 3 ml/min. Fractions containing the major peak were pooled and concentrated to afford [3-(4-bromophenylureido)propyl][(1*S*)-1-phenylethyl][3-(carboxy)propyl]ethylammonium trifluoroacetate (6 mg, 20%): MS(ES^+) m/e 492 $[M-CF_3COO]^+$; ^1H NMR (400 MHz, CD_3OD) δ7.63 (m, 2H), 7.45 (m, 3H), 7.39 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 3.47 (m, 3H), 3.38 (m, 4H), 3.26 (m, 2H), 2.41 (m, 2H), 1.96 (m, 4H), 1.83 (d, J = 6.8 Hz, 3H), 1.30 (m, 3H).

Compound 316, [3-(4-Bromophenylureido)propyl][(1*R*)-1-phenylethyl][3-(carboxy)propyl]ethylammonium trifluoroacetate, can be obtained in an analogous manner to that described for compound 315 and contains the following characteristics: MS(ES^+) m/e 492 $[M-CF_3COO]^+$; ^1H NMR (400 MHz, CD_3OD) δ7.63 (m, 2H), 7.45 (m, 3H), 7.39

(d, J = 9.0 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 3.47 (m, 3H), 3.37 (m, 4H), 3.26 (m, 2H), 2.41 (m, 2H), 1.96 (m, 4H), 1.83 (d, J = 6.8 Hz, 3H), 1.31 (m, 3H).

Example 21. Synthesis of [3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(carboxy)benzyl]ethylammonium iodide (Compound 322)

The following synthesis is depicted in Scheme 21.

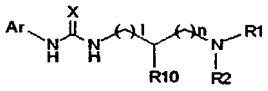
Lithium hydroxide monohydrate (4 mg, 0.095 mmol) was added to a solution of [3-(phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(methoxycarbonyl)benzyl]ethylammonium iodide (28 mg, 0.044 mmol) in 10% water/methanol (1.3 ml). After stirring at RT for 26 h, the reaction mixture was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 33% methanol/chloroform to afford [3-(phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(carboxy)benzyl]ethylammonium iodide (19 mg, 70%): MS(ES^+) m/e 496 $[M-I]^+$; ^1H NMR (400 MHz, CD_3OD) δ8.01 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.38 (m, 2H), 7.30 (m, 4H), 7.24 (m, 2H), 6.97 (m, 1H), 4.59 (s, 2H), 3.31 (m, 8H), 3.15 (m, 2H), 2.15 (m, 2H), 1.48 (t, J = 7.1 Hz, 3H).

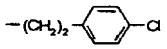
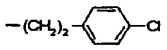
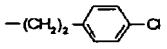
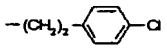
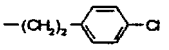
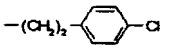
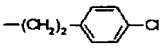
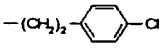
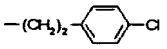
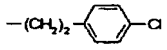
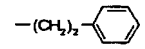
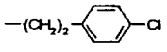
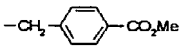
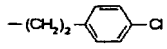
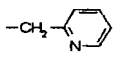
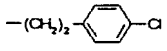
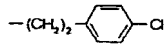
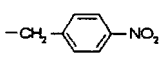
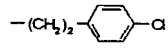
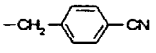
Abbreviations:

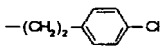
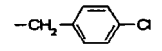
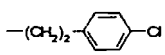
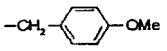
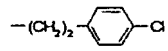
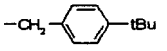
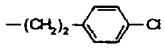
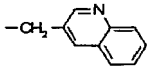
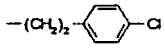
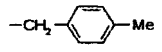
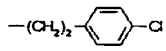
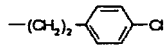
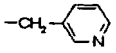
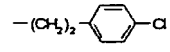
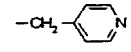
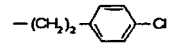
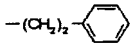
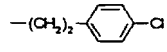
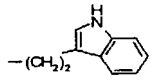
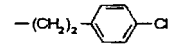
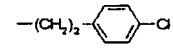
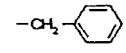
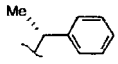
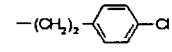
EtOH	ethanol
CH_2Cl_2	dichloromethane
DMSO	dimethylsulfoxide
MeOH	methanol
HOAc	acetic acid
DIEA	diisopropylethylamine
DCM	dichloromethane
DMF	N,N-dimethylformamide
BAP	borane and pyridine
TBAI	tetrabutylammonium iodide
$SnCl_2$	tin chloride
Fmoc	9*H*-9-fluorenylmethoxycarbonyl
Asp	aspartic acid residue
tBu	*tert*-butyl
WSC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
HOBt	1-hydroxybenzotriazole
THF	tetrahydrofuran
TFA	trifluoroacetic acid
DMAP	4-(dimethylamino)pyridine

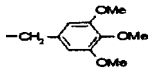
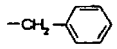
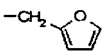
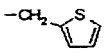
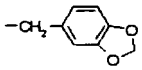
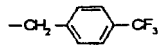
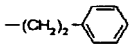
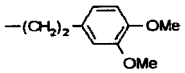
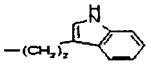
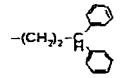
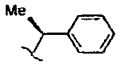
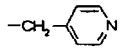
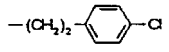
Table 1a and 1b list a variety of compounds that can be synthesized by using one of the methods described above.

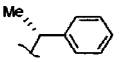
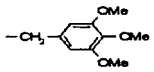
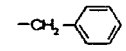
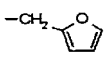
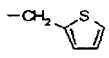
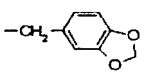
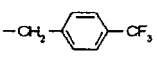
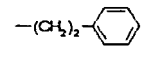
Table 1a

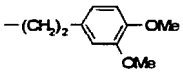
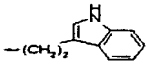
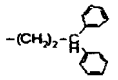
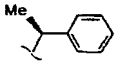
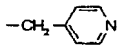
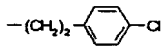
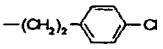


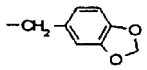
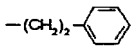
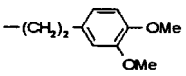
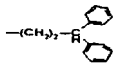
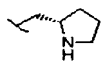
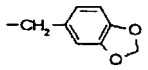
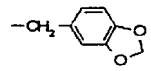
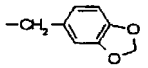
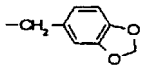
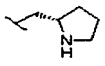
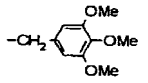
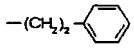
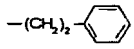
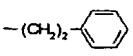
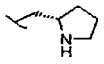
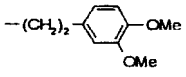
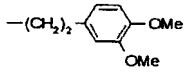
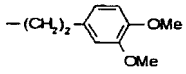
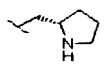
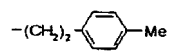
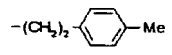
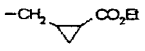
CPD No.	Ar	X	l	n	R1	R2	R10	Mass Spec. m/e		
1	phenyl	O	1	1		ethyl	H	ES^+	360	$[M+H]^+$
2	4-nitrophenyl	O	1	1		ethyl	H	FD	405	$[M+H]^+$
3	4-bromophenyl	O	1	1		ethyl	H	ES^+	438	$[M+H]^+$
4	4-nitrophenyl	O	1	0		ethyl	H	ES^+	391	$[M+H]^+$
5	4-nitrophenyl	O	1	2		ethyl	H	ES^-	417	$[M-H]^-$
6	4-chlorophenyl	O	1	1		ethyl	H	ES^-	392	$[M-H]^-$
7	phenyl	O	1	2		ethyl	H	ES^+	374	$[M+H]^+$
8	phenyl	O	1	3		ethyl	H	ES^+	388	$[M+H]^+$
9	2-methoxy-phenyl	O	1	1		ethyl	H	ES^+	390	$[M+H]^+$
10	phenyl	O	1	1		n-propyl	H	ES^+	374	$[M+H]^+$
11	phenyl	O	1	1		ethyl	H	ES^+	326	$[M+H]^+$
12	phenyl	O	1	1			H	ES^+	480	$[M+H]^+$
13	phenyl	O	1	1			H	FD	422	M^+
14	phenyl	O	1	1		n-butyl	H	ES^+	388	$[M+H]^+$
15	phenyl	O	1	1			H	ES^+	467	$[M+H]^+$
16	phenyl	O	1	1			H	ES^+	447	$[M+H]^+$

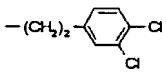
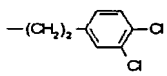
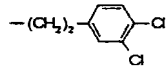
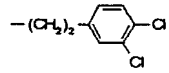
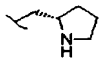
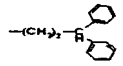
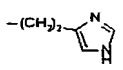
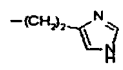
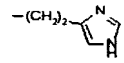
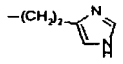
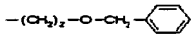
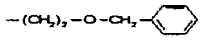
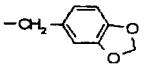
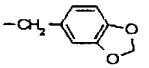
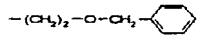
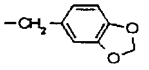
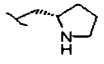
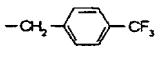
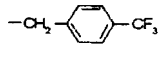
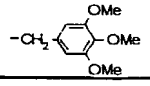
17	phenyl	O	1	1			H	ES^+	456	$[M+H]^+$
18	phenyl	O	1	1			H	ES^+	452	$[M+H]^+$
19	phenyl	O	1	1			H	ES^+	478	$[M+H]^+$
20	phenyl	O	1	1			H	ES^+	473	$[M+H]^+$
21	phenyl	O	1	1			H	ES^+	436	$[M+H]^+$
22	phenyl	O	1	1			H	ES^+	484	$[M+H]^+$
23	phenyl	O	1	1			H	ES^+	423	$[M+H]^+$
24	phenyl	O	1	1			H	ES^+	423	$[M+H]^+$
25	phenyl	O	1	1			H	ES^+	436	$[M+H]^+$
26	phenyl	O	1	1			H	ES^+	475	$[M+H]^+$
27	phenyl	O	1	1		methyl	H	ES^+	346	$[M+H]^+$
28	phenyl	O	1	1			H	ES^+	422	$[M+H]^+$
29	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	FD	502	$[M+H]^+$
30	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	476	$[M+H]^+$
31	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	510	$[M+H]^+$
32	4-bromophenyl	O	1	2		$-(CH_2)_3CO_2Me$	H	ES^+	516	$[M+H]^+$
33	4-bromophenyl	O	1	3		$-(CH_2)_3CO_2Me$	H	ES^+	530	$[M+H]^+$
34	4-methylphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	438	$[M+H]^+$

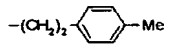
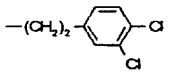
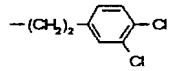
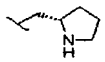
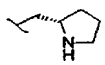
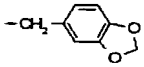
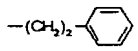
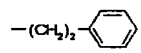
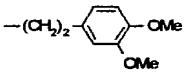
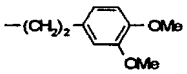
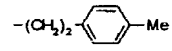
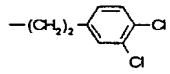
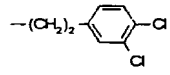
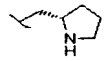
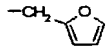
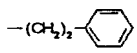
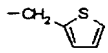
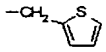
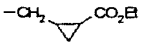
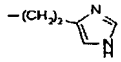
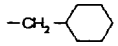
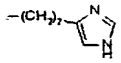
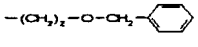
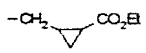
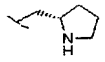
35	3,4-dichloro-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	492	$[M+H]^+$
36	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	522	$[M+H]^+$
37	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	462	$[M+H]^+$
38	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	452	$[M+H]^+$
39	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	468	$[M+H]^+$
40	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	506	$[M+H]^+$
41	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	528	$[M+H]^+$
42	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	475	$[M+H]^+$
43	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	536	$[M+H]^+$
44	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	515	$[M+H]^+$
45	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	552	$[M+H]^+$
46	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	566	$[M+H]^+$
47	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	476	$[M+H]^+$
48	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	463	$[M+H]^+$
49	phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	432	$[M+H]^+$
50	4-bromophenyl	O	1	0		$-(CH_2)_3CO_2Me$	H	ES^+	488	$[M+H]^+$
51	3-chlorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	458	$[M+H]^+$
52	3-methylphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	438	$[M+H]^+$
53	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	526	$[M+H]^+$

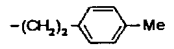
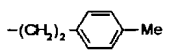
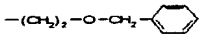
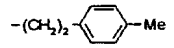
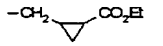
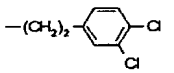
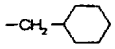
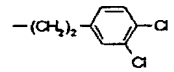
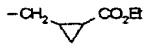
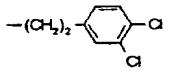
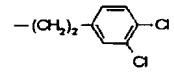
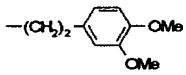
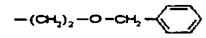
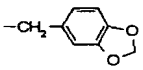
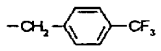
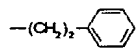
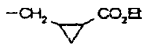
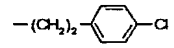
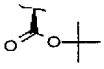
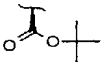
54	2-biphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	500	$[M+H]^+$
55	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	484	$[M+H]^+$
56	phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	424	$[M+H]^+$
57	4-methoxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	454	$[M+H]^+$
58	4-phenoxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	516	$[M+H]^+$
59	1-naphthyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	474	$[M+H]^+$
60	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	488	$[M+H]^+$
61	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	462	$[M+H]^+$
62	4-bromophenyl	O	1	2		$-(CH_2)_3CO_2H$	H	ES^+	502	$[M+H]^+$
63	4-bromophenyl	O	1	3		$-(CH_2)_3CO_2H$	H	ES^+	516	$[M+H]^+$
64	4-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	424	$[M+H]^+$
65	3,4-dichloro-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	478	$[M+H]^+$
66	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	538	$[M+H]^+$
67	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	448	$[M+H]^+$
68	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	438	$[M+H]^+$
69	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	454	$[M+H]^+$
70	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	492	$[M+H]^+$
71	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	516	$[M+H]^+$
72	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	462	$[M+H]^+$

73	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	522	$[M+H]^+$
74	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	501	$[M+H]^+$
75	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	538	$[M+H]^+$
76	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	552	$[M+H]^+$
77	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	462	$[M+H]^+$
78	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^-	447	$[M-H]^-$
79	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	496	$[M+H]^+$
80	phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	418	$[M+H]^+$
81	4-bromophenyl	O	1	0		$-(CH_2)_3CO_2H$	H	ES^+	474	$[M+H]^+$
82	3-chlorophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	444	$[M+H]^+$
83	3-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	424	$[M+H]^+$
84	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	512	$[M+H]^+$
85	2-biphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	486	$[M+H]^+$
86	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	470	$[M+H]^+$
87	phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	410	$[M+H]^+$
88	4-methoxyphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	440	$[M+H]^+$
89	4-phenoxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	502	$[M+H]^+$
90	1-naphthyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	460	$[M+H]^+$
93	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		ethyl	H	ES^+	454	$[M+H]^+$

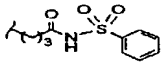
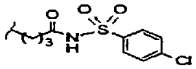
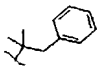
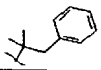
94	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	518	$[M+H]^+$
95	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	456	$[M+H]^+$
96	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	516	$[M+H]^+$
97	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	576	$[M+H]^+$
98	2-biphenyl	O	1	1			H	ES^+	483	$[M+H]^+$
99	2-biphenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H	ES^+	474	$[M+H]^+$
100	2-biphenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	492	$[M+H]^+$
101	2-biphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	490	$[M+H]^+$
102	2-biphenyl	O	1	1			H	ES^+	487	$[M+H]^+$
103	2-biphenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	538	$[M+H]^+$
104	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	506	$[M+H]^+$
105	2-biphenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	462	$[M+H]^+$
106	2-biphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	474	$[M+H]^+$
107	2-biphenyl	O	1	1			H	ES^+	457	$[M+H]^+$
108	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	490	$[M+H]^+$
109	2-biphenyl	O	1	1			H	ES^+	560	$[M+H]^+$
110	2-biphenyl	O	1	1			H	ES^+	517	$[M+H]^+$
111	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	444	$[M+H]^+$
112	2-biphenyl	O	1	1			H	ES^+	514	$[M+H]^+$

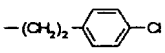
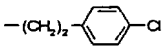
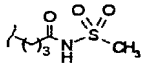
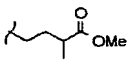
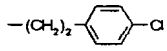
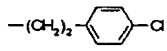
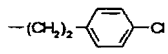
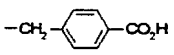
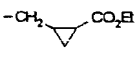
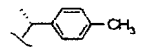
113	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	498	$[M+H]^+$
114	2-biphenyl	O	1	1			H	ES^+	546	$[M+H]^+$
115	2-biphenyl	O	1	1			H	ES^+	568	$[M+H]^+$
116	2-biphenyl	O	1	1			H	ES^+	525	$[M+H]^+$
117	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	520	$[M+H]^+$
118	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	422	$[M+H]^+$
119	4-bromophenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H	ES^+	436	$[M+H]^+$
120	4-bromophenyl	O	1	1			H	ES^+	470	$[M+H]^+$
121	4-bromophenyl	O	1	1			H	ES^+	500	$[M+H]^+$
122	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	458	$[M+H]^+$
123	4-bromophenyl	O	1	1			H	ES^+	536	$[M+H]^+$
124	4-bromophenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	490	$[M+H]^+$
125	4-bromophenyl	O	1	1			H	ES^+	528	$[M+H]^+$
126	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	462	$[M+H]^+$
127	4-bromophenyl	O	1	1			H	ES^+	540	$[M+H]^+$
128	4-bromophenyl	O	1	1			H	ES^+	489	$[M+H]^+$
129	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	486	$[M+H]^+$
130	4-bromophenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	518	$[M+H]^+$
131	4-bromophenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H	ES^+	522	$[M+H]^+$

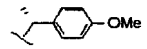
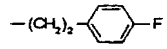
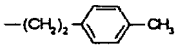
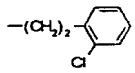
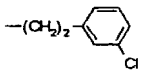
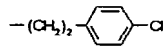
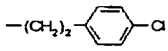
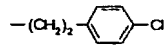
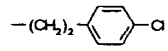
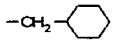
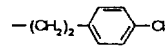
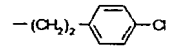
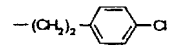
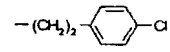
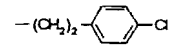
132	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	476	$[M+H]^+$
133	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	530	$[M+H]^+$
134	4-bromophenyl	O	1	1			H	ES^+	527	$[M+H]^+$
135	3-methylphenyl	O	1	1			H	ES^+	421	$[M+H]^+$
136	3-methylphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	398	$[M+H]^+$
137	3-methylphenyl	O	1	1		ethyl	H	ES^+	340	$[M+H]^+$
138	3-methylphenyl	O	1	1			H	ES^+	438	$[M+H]^+$
139	3-methylphenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	460	$[M+H]^+$
140	3-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	458	$[M+H]^+$
141	3-methylphenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	414	$[M+H]^+$
142	3-methylphenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	468	$[M+H]^+$
143	3-methylphenyl	O	1	1			H	ES^+	463	$[M+H]^+$
144	3-chlorophenyl	O	1	1			H	ES^+	412	$[M+H]^+$
145	3-chlorophenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H	ES^+	394	$[M+H]^+$
146	3-chlorophenyl	O	1	1			H	ES^+	450	$[M+H]^+$
147	3-chlorophenyl	O	1	1			H	ES^+	418	$[M+H]^+$
148	3-chlorophenyl	O	1	1			H	ES^+	456	$[M+H]^+$
149	3-chlorophenyl	O	1	1			H	ES^+	484	$[M+H]^+$
150	3-chlorophenyl	O	1	1			H	ES^+	441	$[M+H]^+$

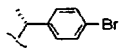
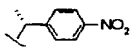
151	3-chlorophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	402	$[M+H]^+$
152	3-chlorophenyl	O	1	1			H	ES^+	480	$[M+H]^+$
153	3-chlorophenyl	O	1	1			H	ES^+	472	$[M+H]^+$
154	3-chlorophenyl	O	1	1			H	ES^+	496	$[M+H]^+$
155	3-chlorophenyl	O	1	1			H	ES^+	526	$[M+H]^+$
156	3-chlorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	500	$[M+H]^+$
157	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	472	$[M+H]^+$
158	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3SMe$	H	ES^+	514	$[M+H]^+$
159	4-methoxy-phenyl	O	1	1			H	ES^+	522	$[M+H]^+$
160	3,4-dichloro-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	496	$[M+H]^+$
161	1-naphthyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	488	$[M+H]^+$
162	1-naphthyl	O	1	1			H	ES^+	474	$[M+H]^+$
163	phenyl	O	1	1		ethyl	OH	ES^+	376	$[M+H]^+$
164	4-chlorophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	460	$[M+H]^+$
165	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$		ES^+	588	$[M+H]^+$
166	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$		ES^+	588	$[M+H]^+$
167	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	OH	ES^+	504	$[M+H]^+$
168	4-methoxy-phenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	456	$[M+H]^+$
169	4-benzyloxy-phenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	532	$[M+H]^+$

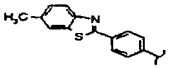
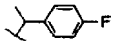
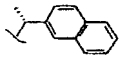
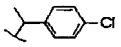
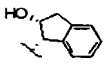
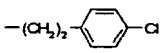
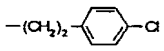
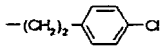
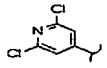
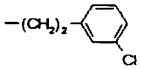
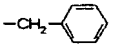
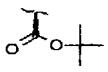
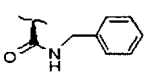
170	4-(trifluoro-methoxy)phenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	510	$[M+H]^+$
171	4-chlorophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	444	$[M+H]^+$
172	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	490	$[M+H]^+$
173	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	476	$[M+H]^+$
174	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	490	$[M+H]^+$
175	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	476	$[M+H]^+$
176	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	488	$[M+H]^+$
177	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	476	$[M+H]^+$
178	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	490	$[M+H]^+$
179	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	476	$[M+H]^+$
180	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	504	$[M+H]^+$
181	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	490	$[M+H]^+$
182	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	504	$[M+H]^+$
183	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	490	$[M+H]^+$
184	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Et$	H	ES^+	516	$[M+H]^+$
185	4-chlorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	458	$[M+H]^+$
186	4-bromophenyl	O	1	1		$-CH_2CO_2H$	H	ES^+	460	$[M+H]^+$
187	4-fluorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	442	$[M+H]^+$
188	4-fluorophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	428	$[M+H]^+$

189	2-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	504	$[M+H]^+$
190	2-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	490	$[M+H]^+$
191	4-bromophenyl	O	1	1		ethyl	H	ES^+	430	$[M+H]^+$
192	phenyl	O	1	1		ethyl	H	ES^+	352	$[M+H]^+$
193	4-bromophenyl	O	1	1		$-(CH_2)_3CONH_2$	H	ES^+	487	$[M+H]^+$
194	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	492	$[M+H]^+$
195	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	478	$[M+H]^+$
196	4-bromophenyl	O	1	1			H	ES^+	627	$[M+H]^+$
197	4-bromophenyl	O	1	1			H	ES^+	663	$[M+H]^+$
198	3-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	502	$[M+H]^+$
199	3-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	488	$[M+H]^+$
200	4-bromo-2-methylphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	518	$[M+H]^+$
201	4-bromo-2-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	502	$[M+H]^+$
202	4-bromophenyl	O	1	1		$-(CH_2)_4OCOCH_3$	H	ES^+	516	$[M+H]^+$
203	4-bromophenyl	O	1	1		$-(CH_2)_4OH$	H	ES^+	476	$[M+H]^+$
204	4-bromophenyl	O	1	1		$-(CH_2)_5OCOCH_3$	H	ES^+	532	$[M+H]^+$
205	4-bromophenyl	O	1	1		$-(CH_2)_5OH$	H	ES^+	488	$[M+H]^+$
206	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	506	$[M+H]^+$
207	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	492	$[M+H]^+$

208	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	546	$[M+H]^+$
209	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	532	$[M+H]^+$
210	4-bromophenyl	O	1	1			H	ES^+	567	$[M+H]^+$
211	4-bromophenyl	O	1	1		$-(CH_2)_5CO_2H$	H	ES^+	518	$[M+H]^+$
212	4-bromophenyl	O	1	1			H	ES^+	518	$[M+H]^+$
213	4-bromophenyl	O	1	1		$-(CH_2)_4CO_2Me$	H	ES^+	516	$[M+H]^+$
214	4-bromophenyl	O	1	1		$-(CH_2)_4CO_2H$	H	ES^+	504	$[M+H]^+$
215	4-bromophenyl	O	1	1		$-(CH_2)_3OCOCH_3$	H	ES^+	502	$[M+H]^+$
216	4-bromophenyl	O	1	1		$-(CH_2)_3OH$	H	ES^+	460	$[M+H]^+$
217	4-bromophenyl	O	1	1			H	ES^+	756	$[M+H]^+$
218	4-bromophenyl	O	1	1			H	ES^+	514	$[M+H]^+$
219	phenyl	O	1	1		$-(CH_2)_3OH$	H	ES^+	390	$[M+H]^+$
220	phenyl	O	1	1		$-CH_2CONH_2$	H	ES^+	389	$[M+H]^+$
221	phenyl	O	1	1		$-CH_2CH=CH_2$	H	ES^+	372	$[M+H]^+$
222	4-bromophenyl	O	1	1			H	ES^+	528	$[M+H]^+$
223	4-bromophenyl	O	1	1			H	ES^+	538	$[M+H]^+$
224	4-bromophenyl	O	1	1			H	ES^+	530	$[M+H]^+$
225	4-carboxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	468	$[M+H]^+$
226	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	478	$[M+H]^+$

227	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	494	$[M+H]^+$
228	4-(ethoxy-carbonyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	482	$[M+H]^+$
229	4-iodophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	536	$[M+H]^+$
230	phenyl	O	1	1		ethyl	H	ES^+	344	$[M+H]^+$
231	phenyl	O	1	1		ethyl	H	ES^+	340	$[M+H]^+$
232	phenyl	O	1	1		ethyl	H	ES^+	360	$[M+H]^+$
233	phenyl	O	1	1		ethyl	H	ES^+	360	$[M+H]^+$
234	phenyl	O	1	1		ethyl	H	ES^+	338	$[M+H]^+$
235	4-carboxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	454	$[M+H]^+$
236	3-(ethoxy-carbonyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	482	$[M+H]^+$
237	4-(n-butyloxy-carbonyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	510	$[M+H]^+$
238	phenyl	O	1	1			H	ES^+	470	$[M+H]^+$
239	phenyl	O	1	1		$-CH_2CH(CH_3)_2$	H	ES^+	388	$[M+H]^+$
240	phenyl	O	1	1			H	ES^+	429	$[M+H]^+$
241	phenyl	O	1	1		$-(CH_2)_4CO_2Me$	H	ES^+	446	$[M+H]^+$
242	phenyl	O	1	1		$-(CH_2)_5CO_2Et$	H	ES^+	474	$[M+H]^+$
243	phenyl	O	1	1		$-(CH_2)_2CONH_2$	H	ES^+	403	$[M+H]^+$
244	phenyl	O	1	1		$-(CH_2)_2OCOCH_3$	H	ES^+	418	$[M+H]^+$
245	phenyl	O	1	1		$-CH_2CO_2Me$	H	ES^+	404	$[M+H]^+$

246	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	506	$[M+H]^+$
247	3-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	506	$[M+H]^+$
248	3-chlorophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	460	$[M+H]^+$
249	4-iodophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	552	$[M+H]^+$
250	4-methylphenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	440	$[M+H]^+$
251	3,4-dichloro-phenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	494	$[M+H]^+$
252	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	520	$[M+H]^+$
253	3-bromophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	520	$[M+H]^+$
254	3-chlorophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	474	$[M+H]^+$
255	4-iodophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	566	$[M+H]^+$
256	3,4-dichloro-phenyl	S	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	508	$[M+H]^+$
257	4-fluorophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	444	$[M+H]^+$
258	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	542	$[M+H]^+$
259	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	509	$[M+H]^+$
260	3-cyanophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	435	$[M+H]^+$
261	3-methoxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	440	$[M+H]^+$
262	3-acetylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	452	$[M+H]^+$
263	3-(methylthio) phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	456	$[M+H]^+$
264	4-methylthio-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	456	$[M+H]^+$

265	2-naphthyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	460	$[M+H]^+$
266	4-(trifluoro-methoxy)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	494	$[M+H]^+$
267		O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	557	$[M+H]^+$
268	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	512	$[M+H]^+$
269	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	482	$[M+H]^+$
270	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	512	$[M+H]^+$
271	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	478	$[M+H]^+$
272	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	498	$[M+H]^+$
273	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	492	$[M+H]^+$
274	phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H	ES^+	432	$[M+H]^+$
275	phenyl	O	1	1		$-(CH_2)_2OCH_3$	H	ES^+	390	$[M+H]^+$
276	phenyl	O	1	1		$-CH(CH_3)_2$	H	ES^+	374	$[M+H]^+$
277	4-biphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	486	$[M+H]^+$
278	4-acetylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	474	$[M+Na]^+$
279		O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	479	$[M+H]^+$
280	phenyl	O	1	1			H	ES^+	422	$[M+H]^+$
281	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2Me$		ES^+	602	$[M+H]^+$
282	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2Me$		ES^+	587	$[M+H]^+$
283	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2Me$		ES^+	635	$[M+H]^+$

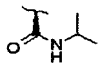
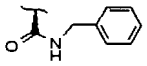
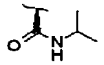
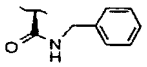
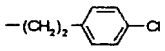
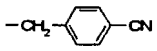
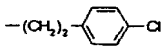
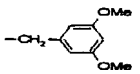
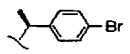
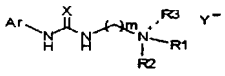
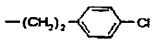
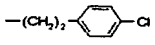
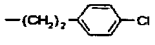
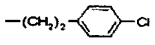
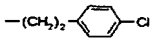
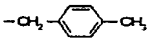
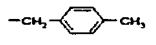
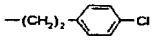
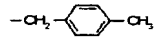
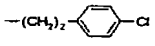
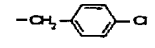
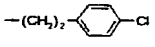
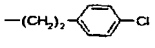
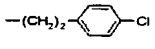
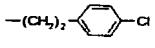
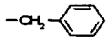
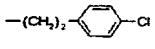
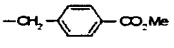
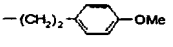
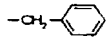
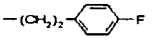
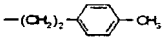
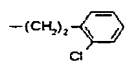
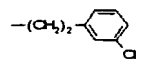
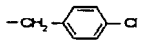
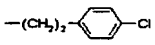
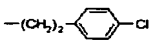
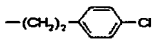
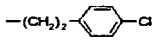
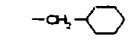
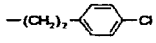
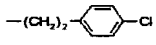
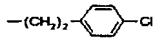
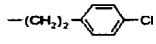
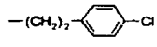
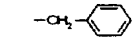
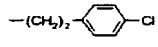
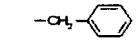
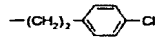
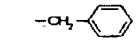
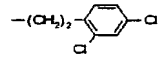
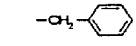
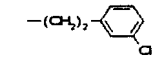
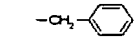
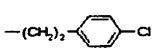
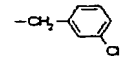
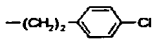
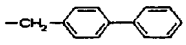
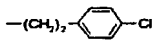
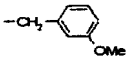
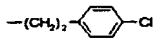
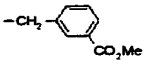
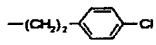
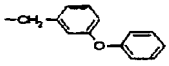
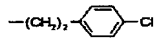
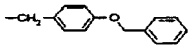
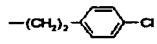
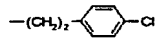
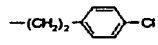
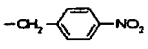
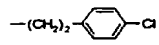
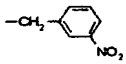
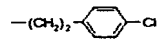
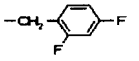
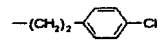
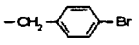
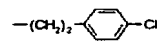
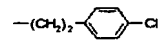
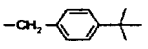
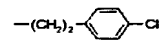
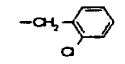
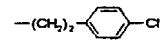
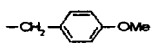
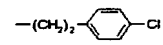
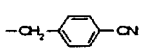
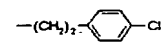
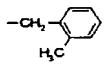
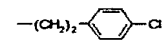
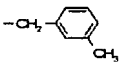
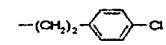
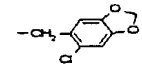
284	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$		ES^+	573	$[M+H]^+$
285	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$		ES^+	621	$[M+H]^+$
286	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$		ES^+	573	$[M+H]^+$
287	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$		ES^+	621	$[M+H]^+$
288	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	490	$[M+H]^+$
289	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	478	$[M+H]^+$
290	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H	ES^+	504	$[M+H]^+$
291	phenyl	O	1	1			H	ES^+	447	$[M+H]^+$
292	phenyl	O	1	1			H	ES^+	482	$[M+H]^+$
293	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H	ES^+	542	$[M+H]^+$

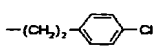
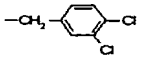
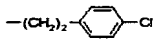
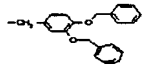
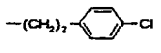
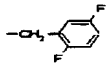
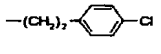
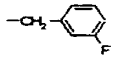
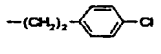
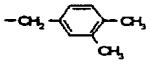
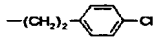
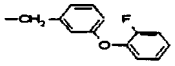
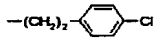
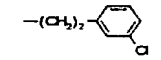
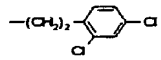
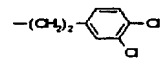
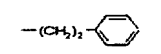
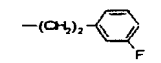
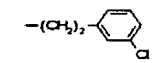
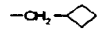
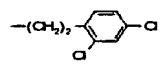
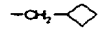
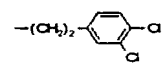
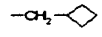
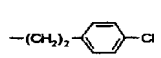
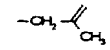
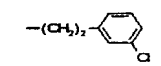
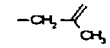
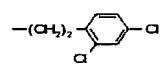
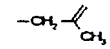
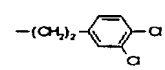
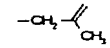
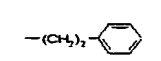
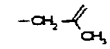
Table 1b

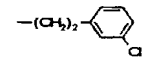
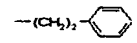
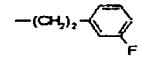
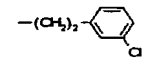
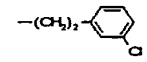
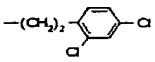
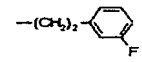
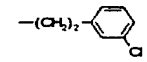
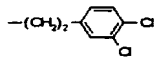
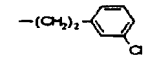
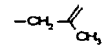
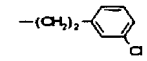
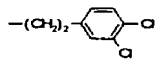
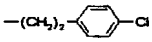
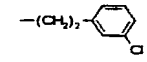
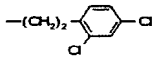
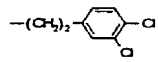
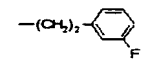
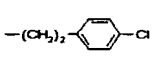
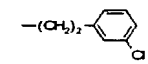
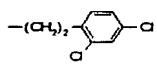


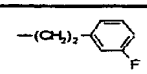
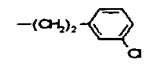
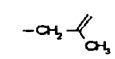
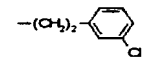
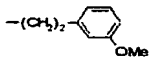
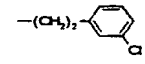
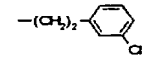
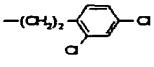
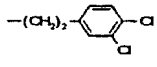
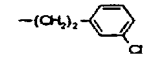
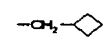
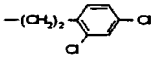
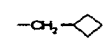
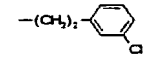
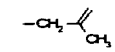
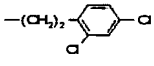
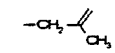
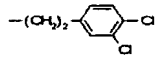
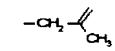
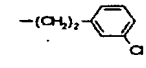
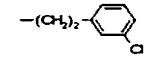
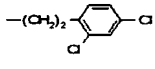
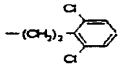
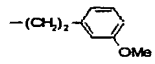
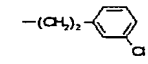
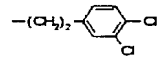
CPD No.	Ar	X	m	R1	R2	R3	Y	Mass Spec. (ES^+) m/e	
91	phenyl	O	3		ethyl	ethyl	I	388	$[M-I]^+$
92	4-bromo-phenyl	O	3		ethyl	ethyl	I	466	$[M-I]^+$
294	4-bromo-phenyl	O	3		n-butyl	ethyl	I	494	$[M-I]^+$
295	4-bromo-phenyl	O	3		n-propyl	ethyl	I	480	$[M-I]^+$
296	phenyl	O	3				Br	540	$[M-Br]^+$
297	phenyl	O	3			ethyl	I	464	$[M-I]^+$
298	phenyl	O	3			ethyl	I	484	$[M-I]^+$
299	phenyl	O	3		$-(CH_2)_3OH$	ethyl	I	418	$[M-I]^+$
300	phenyl	O	3		$-CH_2CONH_2$	ethyl	I	417	$[M-I]^+$
301	phenyl	O	3		$-CH_2CH=CH_2$	ethyl	I	400	$[M-I]^+$
302	phenyl	O	3			ethyl	I	450	$[M-I]^+$
303	phenyl	O	3			ethyl	I	508	$[M-I]^+$
304	phenyl	O	3		ethyl	ethyl	I	384	$[M-I]^+$
305	phenyl	O	3		ethyl	ethyl	I	340	$[M-I]^+$
306	phenyl	O	3		ethyl	ethyl	I	372	$[M-I]^+$
307	phenyl	O	3		ethyl	ethyl	I	368	$[M-I]^+$
308	phenyl	O	3		ethyl	ethyl	I	388	$[M-I]^+$

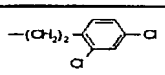
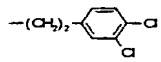
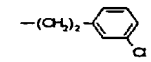
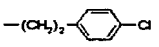
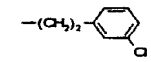
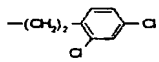
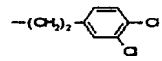
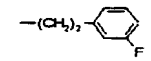
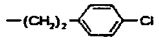
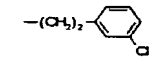
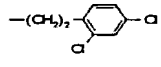
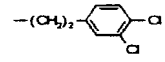
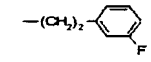
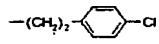
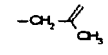
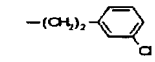
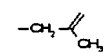
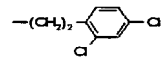
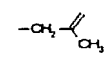
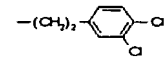
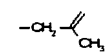
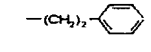
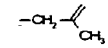
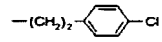
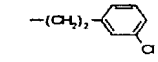
309	phenyl	O	3		ethyl	ethyl	I	388	$[M-I]^+$
310	phenyl	O	3		ethyl	ethyl	I	374	$[M-I]^+$
311	phenyl	O	3		ethyl	ethyl	I	366	$[M-I]^+$
312	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2Me$	ethyl	I	506	$[M-I]^+$
313	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2Me$	ethyl	I	504	$[M-I]^+$
314	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2Me$	ethyl	I	518	$[M-I]^+$
315	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2H$	ethyl	CF_3COO	492	$[M-CF_3COO]^+$
316	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2H$	ethyl	CF_3COO	492	$[M-CF_3COO]^+$
317	phenyl	O	3			ethyl	I	498	$[M-I]^+$
318	phenyl	O	3		$-CH_2CH(CH_3)_2$	ethyl	I	416	$[M-I]^+$
319	phenyl	O	3			ethyl	I	456	$[M-I]^+$
320	phenyl	O	3		$-(CH_2)_4CO_2Me$	ethyl	I	474	$[M-I]^+$
321	phenyl	O	3		$-(CH_2)_5CO_2Et$	ethyl	I	502	$[M-I]^+$
322	phenyl	O	3			ethyl	I	496	$[M-I]^+$
323	phenyl	O	5		ethyl	ethyl	I	416	$[M-I]^+$
324	4-methoxy-phenyl	O	3			ethyl	I	480	$[M-I]^+$
325	3,4-dichloro-phenyl	O	3			ethyl	I	520	$[M-I]^+$
326	4-cyano-phenyl	O	3			ethyl	I	475	$[M-I]^+$
327	phenyl	O	3			ethyl	I	484	$[M-I]^+$
328	phenyl	O	3			ethyl	I	450	$[M-I]^+$

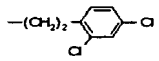
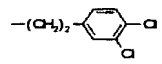
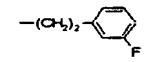
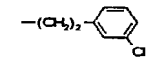
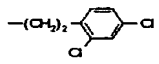
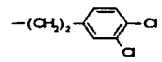
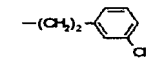
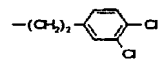
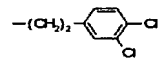
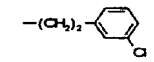
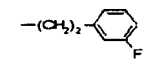
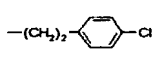
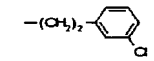
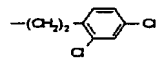
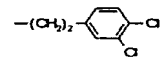
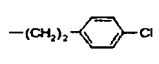
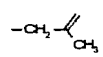
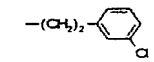
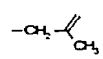
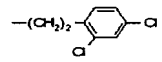
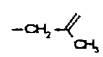
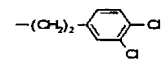
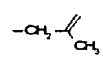
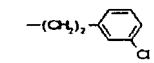
329	phenyl	O	3			ethyl	I	484	$[M-I]^+$
330	phenyl	O	3			ethyl	I	526	$[M-I]^+$
331	phenyl	O	3			ethyl	I	480	$[M-I]^+$
332	phenyl	O	3			ethyl	I	508	$[M-I]^+$
333	phenyl	O	3			ethyl	I	542	$[M-I]^+$
334	phenyl	O	3			ethyl	I	556	$[M-I]^+$
335	4-bromo-phenyl	S	3		ethyl	ethyl	I	482	$[M-I]^+$
336	phenyl	S	3		ethyl	ethyl	I	404	$[M-I]^+$
337	phenyl	O	3			ethyl	I	495	$[M-I]^+$
338	phenyl	O	3			ethyl	I	495	$[M-I]^+$
339	phenyl	O	3			ethyl	I	486	$[M-I]^+$
340	phenyl	O	3			ethyl	I	530	$[M-I]^+$
341	phenyl	O	3			ethyl	I	526	$[M-I]^+$
342	phenyl	O	3			ethyl	I	506	$[M-I]^+$
343	phenyl	O	3			ethyl	I	484	$[M-I]^+$
344	phenyl	O	3			ethyl	I	480	$[M-I]^+$
345	phenyl	O	3			ethyl	I	475	$[M-I]^+$
346	phenyl	O	3			ethyl	I	464	$[M-I]^+$
347	phenyl	O	3			ethyl	I	464	$[M-I]^+$
348	phenyl	O	3			ethyl	I	528	$[M-I]^+$

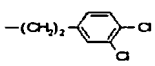
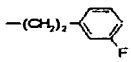
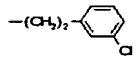
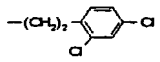
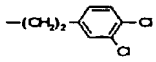
349	phenyl	O	3			ethyl	I	520	$[M-I]^+$
350	phenyl	O	3			ethyl	I	662	$[M-I]^+$
351	phenyl	O	3			ethyl	I	486	$[M-I]^+$
352	phenyl	O	3			ethyl	I	470	$[M-I]^+$
353	phenyl	O	3			ethyl	I	480	$[M-I]^+$
354	phenyl	O	3			ethyl	I	562	$[M-I]^+$
355	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	530	$[M-I]^+$
356	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	530	$[M-I]^+$
357	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	564	$[M-I]^+$
358	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	564	$[M-I]^+$
359	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	496	$[M-I]^+$
360	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	514	$[M-I]^+$
361	3,4-dichloro-phenyl	O	3			ethyl	I	496	$[M-I]^+$
362	3,4-dichloro-phenyl	O	3			ethyl	I	530	$[M-I]^+$
363	3,4-dichloro-phenyl	O	3			ethyl	I	530	$[M-I]^+$
364	3,4-dichloro-phenyl	O	3			ethyl	I	482	$[M-I]^+$
365	3,4-dichloro-phenyl	O	3			ethyl	I	482	$[M-I]^+$
366	3,4-dichloro-phenyl	O	3			ethyl	I	516	$[M-I]^+$
367	3,4-dichloro-phenyl	O	3			ethyl	I	516	$[M-I]^+$
368	3,4-dichloro-phenyl	O	3			ethyl	I	448	$[M-I]^+$

369	3,4-dichloro-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	474	[M-I]$^+$
370	3,4-dichloro-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	440	[M-I]$^+$
371	3,4-dichloro-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	458	[M-I]$^+$
372	4-bromo-phenyl	O	3		-CH$_2$CN	ethyl	I	477	[M-I]$^+$
373	4-bromo-phenyl	O	3		-(CH$_2$)$_2$O(CH$_2$)$_2$OMe	ethyl	I	540	[M-I]$^+$
374	4-bromo-phenyl	O	3		-(CH$_2$)$_2$O(CH$_2$)$_2$OMe	ethyl	I	574	[M-I]$^+$
375	4-bromo-phenyl	O	3		-(CH$_2$)$_2$O(CH$_2$)$_2$OMe	ethyl	I	524	[M-I]$^+$
376	4-bromo-phenyl	O	3			ethyl	I	506	[M-I]$^+$
377	4-bromo-phenyl	O	3			ethyl	I	541	[M-I]$^+$
378	4-bromo-phenyl	O	3			ethyl	I	492	[M-I]$^+$
379	4-bromo-phenyl	O	3		-CH$_2$CH(CH$_2$CH$_3$)$_2$	ethyl	I	522	[M-I]$^+$
380	4-bromo-phenyl	O	3		-CH$_2$CH(CH$_2$CH$_3$)$_2$	ethyl	I	557	[M-I]$^+$
381	4-bromo-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	484	[M-I]$^+$
382	4-bromo-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	484	[M-I]$^+$
383	4-bromo-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	518	[M-I]$^+$
384	4-bromo-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	518	[M-I]$^+$
385	4-bromo-phenyl	O	3		-(CH$_2$)$_2$F	ethyl	I	468	[M-I]$^+$
386	4-(trifluoro-methyl)phenyl	O	3		-(CH$_2$)$_2$O(CH$_2$)$_2$OMe	ethyl	I	530	[M-I]$^+$
387	4-(trifluoro-methyl)phenyl	O	3		-(CH$_2$)$_2$O(CH$_2$)$_2$OMe	ethyl	I	530	[M-I]$^+$
388	4-(trifluoro-methyl)phenyl	O	3		-(CH$_2$)$_2$O(CH$_2$)$_2$OMe	ethyl	I	564	[M-I]$^+$

389	4-(trifluoro-methyl)phenyl	O	3		-$(CH_2)_2O(CH_2)_2OMe$	ethyl	I	514	$[M-I]^+$
390	4-(trifluoro-methyl)phenyl	O	3			ethyl	I	482	$[M-I]^+$
391	4-(trifluoro-methyl)phenyl	O	3		-$(CH_2)_2F$	ethyl	I	474	$[M-I]^+$
392	4-cyano-phenyl	O	3		-$(CH_2)_2O(CH_2)_2OMe$	ethyl	I	483	$[M-I]^+$
393	4-cyano-phenyl	O	3		-$(CH_2)_2CH(CH_3)_2$	ethyl	I	455	$[M-I]^+$
394	4-cyano-phenyl	O	3		-$(CH_2)_2O(CH_2)_2OMe$	ethyl	I	487	$[M-I]^+$
395	4-cyano-phenyl	O	3		-$(CH_2)_2O(CH_2)_2OMe$	ethyl	I	521	$[M-I]^+$
396	4-cyano-phenyl	O	3		-$(CH_2)_2O(CH_2)_2OMe$	ethyl	I	521	$[M-I]^+$
397	4-cyano-phenyl	O	3			ethyl	I	453	$[M-I]^+$
398	4-cyano-phenyl	O	3			ethyl	I	487	$[M-I]^+$
399	4-cyano-phenyl	O	3			ethyl	I	439	$[M-I]^+$
400	4-cyano-phenyl	O	3			ethyl	I	473	$[M-I]^+$
401	4-cyano-phenyl	O	3			ethyl	I	473	$[M-I]^+$
402	4-cyano-phenyl	O	3		-$CH_2CH(CH_2CH_3)_2$	ethyl	I	469	$[M-I]^+$
403	4-cyano-phenyl	O	3		-$(CH_2)_2F$	ethyl	I	431	$[M-I]^+$
404	4-cyano-phenyl	O	3		-$(CH_2)_2F$	ethyl	I	465	$[M-I]^+$
405	4-cyano-phenyl	O	3		-$(CH_2)_2F$	ethyl	I	465	$[M-I]^+$
406	phenyl	O	3		-$(CH_2)_2O(CH_2)_2OMe$	ethyl	I	458	$[M-I]^+$
407	phenyl	O	3		-$(CH_2)_2CH(CH_3)_2$	ethyl	I	430	$[M-I]^+$
408	phenyl	O	3		-$(CH_2)_2CH(CH_3)_2$	ethyl	I	464	$[M-I]^+$

409	phenyl	O	3		$-CH_2CONH_2$	ethyl	I	451	$[M-I]^+$
410	phenyl	O	3		$-CH_2CONH_2$	ethyl	I	451	$[M-I]^+$
411	phenyl	O	3		$-CH_2CN$	ethyl	I	399	$[M-I]^+$
412	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	462	$[M-I]^+$
413	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	462	$[M-I]^+$
414	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	496	$[M-I]^+$
415	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	496	$[M-I]^+$
416	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	446	$[M-I]^+$
417	phenyl	O	3			ethyl	I	428	$[M-I]^+$
418	phenyl	O	3			ethyl	I	428	$[M-I]^+$
419	phenyl	O	3			ethyl	I	462	$[M-I]^+$
420	phenyl	O	3			ethyl	I	462	$[M-I]^+$
421	phenyl	O	3			ethyl	I	412	$[M-I]^+$
422	phenyl	O	3			ethyl	I	414	$[M-I]^+$
423	phenyl	O	3			ethyl	I	414	$[M-I]^+$
424	phenyl	O	3			ethyl	I	448	$[M-I]^+$
425	phenyl	O	3			ethyl	I	448	$[M-I]^+$
426	phenyl	O	3			ethyl	I	380	$[M-I]^+$
427	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	444	$[M-I]^+$
428	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	444	$[M-I]^+$

429	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	478	$[M-I]^+$
430	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	478	$[M-I]^+$
431	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	428	$[M-I]^+$
432	phenyl	O	3		$-(CH_2)_2F$	ethyl	I	406	$[M-I]^+$
433	phenyl	O	3		$-(CH_2)_2F$	ethyl	I	440	$[M-I]^+$
434	phenyl	O	3		$-(CH_2)_2F$	ethyl	I	440	$[M-I]^+$
435	4-methoxy-phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I	460	$[M-I]^+$
436	4-methoxy-phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I	494	$[M-I]^+$
437	4-methoxy-phenyl	O	3		$-CH_2CONH_2$	ethyl	I	481	$[M-I]^+$
438	4-methoxy-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	492	$[M-I]^+$
439	4-methoxy-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I	476	$[M-I]^+$
440	4-methoxy-phenyl	O	3			ethyl	I	458	$[M-I]^+$
441	4-methoxy-phenyl	O	3			ethyl	I	458	$[M-I]^+$
442	4-methoxy-phenyl	O	3			ethyl	I	492	$[M-I]^+$
443	4-methoxy-phenyl	O	3			ethyl	I	492	$[M-I]^+$
444	4-methoxy-phenyl	O	3			ethyl	I	444	$[M-I]^+$
445	4-methoxy-phenyl	O	3			ethyl	I	444	$[M-I]^+$
446	4-methoxy-phenyl	O	3			ethyl	I	478	$[M-I]^+$
447	4-methoxy-phenyl	O	3			ethyl	I	478	$[M-I]^+$
448	4-methoxy-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	474	$[M-I]^+$

449	4-methoxy-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	508	$[M-I]^+$
450	4-methoxy-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I	458	$[M-I]^+$
451	4-methoxy-phenyl	O	3		$-(CH_2)_2F$	ethyl	I	436	$[M-I]^+$
452	4-methoxy-phenyl	O	3		$-(CH_2)_2F$	ethyl	I	470	$[M-I]^+$
453	4-methoxy-phenyl	O	3		$-(CH_2)_2F$	ethyl	I	470	$[M-I]^+$

Example 22. Evaluation of CCR-3 Inhibition Using a Calcium Mobilization Assay

The CCR-3 inhibitory activity of the disclosed compounds was determined by measuring the inhibition of eotaxin-induced calcium mobilization using the assay described below. Compounds 93-162 used in this assay were synthesized by using the method described in Example 6, and Compounds 168-170 were synthesized by using the method described in Example 6 except for the use of isothiocyanates instead of isocyanates in step 6.

CCR-3 transfectant cells (CCR3/HEK293) were isolated and resuspended with assay buffer (20 mM HEPES, 125 mM NaCl, 5 mM KCl, 0.5 mM glucose, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1 % BSA). After washing CCR3/HEK293 cells with assay buffer, cells were loaded with Fura-2/AM in assay buffer for 1 hour at room temperature. Cells were washed and resuspended with assay buffer at 5 x 10^6 cells/ml in assay buffer, and placed in a tissue culture plate (Falcon, no. 3296). Test compounds dissolved in DMSO were added to the wells, followed by eotaxin (10 nM at final concentration). Cells were excited at 340 nm and 380 nm in a fluorimeter (ARGUS50,FDSS2000, Hamamatsu Photonics) and the relative ratio of the fluorescence emitted at 510 nm was recorded. For a control, DMSO without a test compound was added. Intracellular calcium mobilization was calculated as described in Krogel C. *et al.*, *FEBS Let.* (1989) 243, 41-46.

The results shown in Table 2a and Table 2b indicate that the disclosed compounds inhibit calcium mobilization.

Table 2a

Inhibitory effects of compounds on eotaxin-induced intracellular calcium mobilization

CPD No.	Ca^{2+} mobilization 6.25 μg/ml (inhibition %)
93	50
94	50
95	55
96	53
97	57
98	51
99	53
100	53
101	63

102	63
103	53
104	51
105	53
106	57
107	53
108	61
109	51
110	57
111	51
112	52
113	51
114	51
115	57
116	68
117	55
118	58
119	62
120	57
121	52
122	66
123	53
124	55
125	65
126	54
127	59
128	55
129	50
130	51
131	52
132	55
133	63
134	59
135	57
136	63
137	50
138	56
139	65
140	54
141	53
142	58

143	64
144	51
145	53
146	52
147	51
148	57
149	56
150	70
151	54
152	54
153	59
154	55
155	69
156	63
157	53
158	50
159	51
160	58
161	51
162	50
168	23
169	48
170	45

Table 2b

Inhibitory effects of compounds on eotaxin-induced intracellular calcium mobilization

CPD No.	Ca^{2+} mobilization 1.25 μg/ml (inhibition %)
355	63
356	57
357	57
358	63
361	70
362	49
363	56
364	66
365	65
366	46
367	50
393	56
394	76
395	69

396	67
397	69
398	70
399	58
400	68
401	57
435	62
436	57
437	64
438	70
440	62
441	71
442	63
443	69
444	72
445	63
446	76
447	65

Example 23. Evaluation of Eotaxin-induced Chemotaxis of CCR-3 Transfectant Cell

The inhibitory activity of the compounds against eotaxin-induced chemotaxis was determined by measuring the inhibition of migration of CCR-3 transfectant cells (CCR3/U937), using a minor modification of the method described by Ohashi, H. *et al.*, *Int Arch Allergy Immunol.* (1999) 118, 44-50. CCR-3 transfectant cells were grown in RPMI1640 medium containing 10% fetal calf serum (FCS) and Geneticin 418 (0.8 mg/ml). For the assay, CCR-3 transfectant cells were isolated and resuspended at 1 x 10^7 cells/ml in assay medium (RPMI 1640 medium containing 0.1 % bovine serum albumin (BSA)). The chemotaxis assay was performed in a 24-well culture plate. Human eotaxin suspended in assay medium was added to the wells at 1 x 10^{-9} M along with test compounds at various concentrations. For a positive control, eotaxin was added to the wells without a test compound, and for a negative control, neither eotaxin nor a test compound was added to the wells. Chemotaxicell (Kurabo Co., Ltd.) having 5 micrometers pore size were inserted into each well and 100 micro liters of CCR-3 transfectant cells suspension were added to the top chamber. The plates were incubated at 37 °C for 1 hour. After incubation, migrated cells in lower wells were diluted and counted by particle size distribution analyzer (CDP-500, Sysmex Co., Ltd.).

The results shown in Table 3a, 3b. 3c and 3d indicate that the disclosed compounds inhibit eotaxin-induced chemotaxis.

Table 3a

Inhibitory effects of compounds on eotaxin-induced chemotaxis of CCR3 transfectants

CPD No.	Chemotaxis Assay 10 μM (inhibition %)
1	100
2	100
3	100
4	59
5	99
6	100
7	99
8	94
9	100
10	99
11	86
14	97
16	63
17	51
18	58
19	47
20	26
21	40
22	25
23	82
24	100
25	88
27	97
28	76
29	100
30	100
31	97
32	99
33	95
34	96
35	100
36	34
37	100
38	46
39	78
40	88
41	20

42	96
43	50
45	62
47	58
48	34
49	100
50	54
51	100
52	100
53	93
54	19
55	38
56	100
57	100
58	100
59	87
60	98
61	100
62	98
63	100
64	100
65	100
66	32
67	100
68	31
69	81
70	89
71	64
72	68
73	44
74	50
75	68
76	44
77	76
79	78
80	65
81	58
82	100
83	100
84	100
85	19
86	37
87	97
88	100
89	89
90	100

163	96
164	100
165	100
166	100
167	100
171	100
172	100
173	100
174	100
175	100
176	75
177	89
178	100
179	100
180	100
181	100
182	97
183	94
184	100
185	100
186	69
187	100
188	100
189	94
190	90
191	100
192	100
193	100
194	100
195	100
196	100
197	100
198	100
199	100
200	100
201	100
202	100
203	100
204	78
205	97
206	64
207	50
208	63
209	94
210	100
211	67

212	100
213	92
214	99
215	89
216	100
217	87
218	99
219	86
220	77
221	100
222	79
223	86
224	75
225	100
226	100
227	100
228	100
229	100
230	100
231	90
232	100
233	100
234	89
235	91
236	97
237	100
238	69
239	100
240	86
241	100
242	73
243	84
244	81
245	100
246	100
247	99
248	100
249	100
250	99
251	100
252	100
253	74
254	82
255	100
256	100
257	100

258	100
259	100
260	100
261	100
262	62
263	100
264	100
265	95
266	100
267	99
268	100
269	100
270	100
271	100
272	89
273	88
274	60
275	100
276	100
277	76
278	100
279	96
280	60
281	100
282	100
283	100
284	95
285	58
286	100
287	100
288	100
289	100
290	100
291	53
292	56
293	95

Table 3b

Inhibitory effects of compounds on eotaxin-induced chemotaxis of CCR3 transfectants

CPD No.	CCR-3 Transfectant Chemotaxis Assay 6.25 μg/ml (inhibition %)

97	21
99	47
100	54
102	19
106	47
107	55
108	23
109	12
110	32
111	44
112	26
113	66
114	22
115	62
116	82
118	62
119	65
120	34
121	64
122	92
125	90
126	54
128	33
132	11
133	21
135	12
136	32
137	40
138	31
149	31
155	56

Table 3c

Inhibitory effects of compounds on eotaxin-induced chemotaxis of CCR3 transfectants

CPD No.	Chemotaxis Assay 10 μM (inhibition %)
91	100
92	100
294	100

295	100
296	67
297	100
298	100
299	100
300	100
301	100
302	100
303	100
304	66
305	100
306	100
307	92
308	100
309	100
310	100
311	93
312	97
313	86
314	100
315	63
316	82
317	100
318	100
319	100
320	100
321	100
322	93
323	100
324	100
325	100
326	100
327	100
328	100
329	100
330	100
331	100
332	100
333	100
334	100
335	100
336	100
337	99
338	100
339	100
340	100

341	100
342	97
343	100
344	100
345	100
346	100
347	100
348	100
349	100
350	59
351	100
352	100
353	100
354	100

Table 3d

Inhibitory effects of compounds on eotaxin-induced chemotaxis of CCR3 transfectants

CPD No.	Chemotaxis Assay 0.1 μg/ml (inhibition %)
359	49
360	70
368	88
369	82
370	64
371	86
372	76
373	100
374	100
375	91
376	87
377	46
378	81
379	80
380	46
381	68
382	98
383	43
384	76
385	68
386	43
387	94
388	56
389	65

390	51
391	47
392	45
402	71
403	77
404	47
405	57
406	43
407	52
408	74
409	53
410	50
411	42
412	84
413	95
414	98
415	99
416	69
417	59
418	89
419	76
420	99
421	66
422	42
423	92
424	95
425	93
426	44
427	67
428	93
429	64
430	76
431	96
432	96
433	76
434	100
439	51
448	82
449	96
450	35
451	92
452	59
453	87

Example 24. Evaluation of Eotaxin-induced Chemotaxis of Eosinophils

The inhibitory activity of the compounds against eotaxin-mediated chemotaxis of human-derived eosinophils was determined assay described below.

Eosinophils were prepared from culture of human cord blood mononuclear cells as described by Ohashi, H. *et al.*, *Int Arch Allergy Immunol.* (1999) 118, 44-50. For the assay, eosinophils were resuspended at 1 x 10^7 cells/ml in assay medium (RPMI 1640 medium containing 0.1 % bovine serum albumin (BSA)). The chemotaxis assay was performed in a 24-well culture plate. Human eotaxin suspended in assay medium was added into wells at 1 x 10^{-9} M with test compounds at various concentrations. For a positive control, eotaxin was added without a test compound, and for a negative control, neither eotaxin nor a test compound was added to the wells. Chemotaxicell (Kurabo Co., Ltd.) having 5 micrometers pore size were inserted into each well and 100 microliters of eosinophil suspension were added to the top chamber. The plates were incubated at 37 °C for 1 hour. After incubation, migrated cells in lower wells were diluted and counted by particle size distribution analyzer (CDP-500, Sysmex Co., Ltd.).

The results shown in Table 4 indicate that the disclosed compounds inhibit eotaxin-induced chemotaxis in cultured eosinophils.

Table 4.

Inhibitory effects of compounds on Eotaxin-induced chemotaxis of cultured eosinophils.

CPD No.	Cultured Eosinophil Chemotaxis assay 10.00 μM (inhibition %)
1	100
3	100
36	31
38	11
60	100
61	100
65	100
66	44
67	71
91	100
92	100

Example 25. Use of an Urea Derivative to treat a CCR-3 Mediated Disease

A patient suffering from asthma is administered N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound 1). Approximately 1 mmole of the compound is administered to the patient via inhalation of an aerosol comprising compound 1. The amount of compound administered should be between 0.01 and 20 mg/kg of the patient's weight.

Example 26. Suppression of Type II Collagen-induced Arthritis in Mice by Compound No. 60 and Compound No. 298

The inhibitory effects of Compound No. 60 (CPD No.60) and Compound No. 298 (CPD No. 298) on collagen-induced arthritis were evaluated in mice.

Male DBA/1 mice were purchased from Japan Charles River Inc. (Kanagawa, Japan) and used at 5 week of age. Mice were immunized intradermally at the base of the tail with mixture of 100 μg of bovine type II collagen (Collagen Gijyutsu-Kenshukai, Japan) and 100 μg of *Mycobacterium tuberculosis* H37Ra (Difco, Detroit, MI) in incomplete Freaund's adjuvant at the base of the tail, and then boosted 21 days later with same emulsion. The compound to be studied (20 mg/kg per day) was administered subcutaneously starting at 2nd immunization. In the control experiment, control vehicle (10% DMSO and 10% Cremophor EL in saline) was administered instead of the compound to be studied. Clinical scoring for each paw was assessed by reference to the following scale: 0=normal, 1=swelling and/or erythema of one toe, 2=swelling and/or erythema of two or more toes, 3=swelling and erythema of the entire paw, 4=complete sewlling and erythema of the entire paw and incapacity to bend the ankle. Clinical score for the whole animal was expressed as the cumulative value for all paws, with a maximum of 16. Each group consists of 10 animals.

The inhibitory effects of Compound No. 60 and Compound No. 298 on collagen-induced arthritis were shown in Figure 1A and 1B, respectively. A marked prevention in clinical score was observed by administration of Compound No. 60 or Compound No. 298, as opposed to administration of control vehicle.

Example 27. Suppression of Airway Hyperreactivity and Eosinophil Infiltration in Bronchoalveolar Lavage Fluid (BALF) by Compound No. 298

Male BALB/c mice were immunized by an intraperitoneal injection of 10 μg OVA adsorbed to 1 mg aluminum hydroxide gel (alum). A booster injection of the same dose of alum-adsorbed OVA was given 5 days later. Unimmunized control mice received saline.

Twelve days after primary immunization, both the immunized and unimmunized mice were exposed to aerosolized antigen. Aerosolization of OVA was performed using a nose-only aerosol chamber adapted for mice. Animals were exposed for 10 minutes to 5 mg/ml OVA aerosolized by an ultrasonic nebulizer (NE-U12, Omron, Tokyo, Japan) driven by a vacuum pump. The antigen bronchoprovocation was repeated on day 16 and day 20 under the same conditions. Compound No. 298 (CPD No. 298) was dissolved in saline containing 2 % DMSO and 2 % Cremophore and administered intraperitoneally for 9 days, starting on the first day of antigen inhalation.

Twenty-four hours after the final aerosol exposure, bronchoconstriction was measured by the overflow method of Konzett and Rössler. Mice were anesthetized by an intraperitoneal injection of sodium pentobarbitone (50 mg/kg), and the tracheas were surgically exposed, cannulated, and connected to a rodent ventilator (Model 683, Harvard Apparatus, South Natick, MA) and a bronchospasm transducer (Model 7020, Ugo Basile, Comerio-Varese, Italy). Animals were mechanically ventilated with air at 60 strokes/min with a stroke volume of 0.6 ml. A paralytic agent, pancuronium bromide, 0.1 mg/kg, was administered to eliminate spontaneous respiration. After a stable baseline airway pressure was established, acetylcholine chloride was injected intravenously in a volume of 1 μl/g of mouse per dose, starting with 31.3 μg/kg, and increasing the concentration two-fold for each subsequent dose. Bronchoconstriction was recorded on a flatbed recorder (Model FBR-252A, TOA Electronics Ltd., Tokyo, Japan). Bronchoconstriction (%) represent the respiratory overflow volume provoked by acetylcholine as a percentage of the maximal overflow volume (100%) obtained by totally occluding the tracheal cannula. *See* Figure 2A. Inhibition of bronchoconstriction provoked by acetylcholine (Murine Asthma Model) by Compound No. 298 was shown in Figure 2A. In some experiments, airway reactivity was expressed by the area under the dose-response curve (the curves in Figure 2A) of bronchoconstriction against the acetylcholine concentration. *See* Figure 2B.

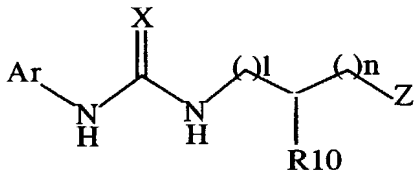
Immediately after the measurement of airway reactivity to acethycholine, BALF was collected by lavaging whole-lung three times with 0.7-ml aliquots of physiological saline containing 0.1% BSA via the tracheal cannula while gently massaging the thorax. The BALF recovered from one mouse was pooled, centrifuged, and the cells were resuspended in 100 μl saline containing 0.1% BSA. Cell numbers were determined using a hemocytometer and 2 x 10^4 cells were cytecetrifuged onto a glass slide. Cells were stained with Diff-Quik (International reagent, Kobe, Japan), and cell types were identified by morphological criteria. Two hundred cells were examined per slide for differential count. *See* Figure 2C. As shown in Figure 2C, Compound No. 298 (CPD No. 298) significantly suppressed eosinophil infiltration to bronchoalveolar lavage fluid (BALF).

The invention has been disclosed broadly and illustrated in reference to representative embodiments described above. Those skilled in the art will recognize that various modifications can be made to the present invention without departing from the spirit and scope thereof.

All references cited herein are hereby incorporated herein by reference in their entireties.

WE CLAIM:

1. A compound having the following Formula:



or a salt, hydrate, or complex thereof, wherein:

l and n are independently 0, 1, 2, 3, 4 or 5;

(l + n) is 1, 2, 3, 4 or 5;

X is O or S;

R10 is selected from the group consisting of hydrogen, hydroxy, C_{3-7}cycloalkyloxy, acyloxy, carboxy, carbamoyl, acyl, amino, alkylamino, arylamino, acylamino, C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl, alkyloxycarbonyl,

Wherein the C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl or alkyloxycarbonyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, acyloxy, C_{1-5}alkoxy, aryloxy, heteroaryloxy, nitro, amino, acylamino, alkylamino, arylamino, cyano, aryl, heteroaryl

Wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-5}alkyl or C_{1-5}alkoxy, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydroxy, and halogen;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5}alkyl, C_{1-}

$_5$alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

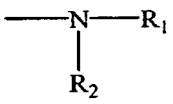
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

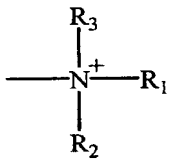
and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

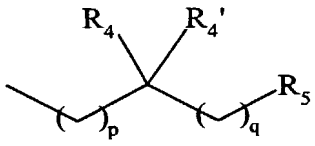
Z is:



or



wherein R_1 is:



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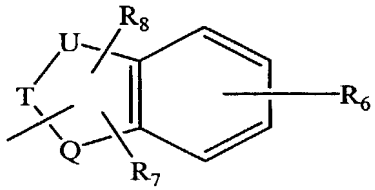

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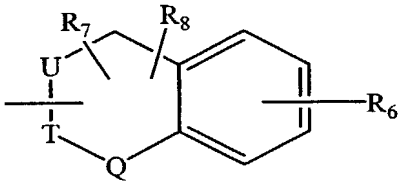
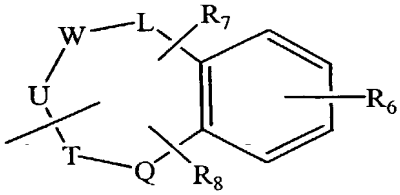


or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl,

isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido,

arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

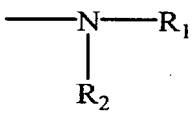
C_{3-7} cycloalkyl

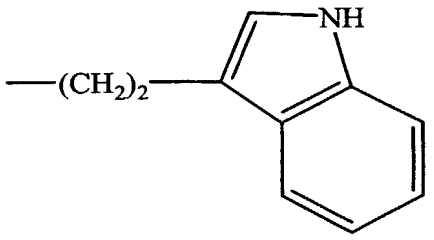
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

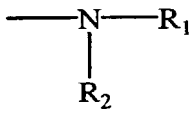
further provided that Ar is not 2-hydroxy-5-methoxyphenyl, and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not .

2. The compound according to claim 1, wherein Z is



.

3. The compound according to claim 2, wherein (l + n) is 2, 3, or 4.

4. The compound according to claim 3, wherein (l + n) is 2, or 3.

5. The compound according to claim 1, wherein X is O.

6. The compound according to claim 5, wherein R10 is hydrogen.

7. The compound according to claim 6, wherein Ar is aryl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy.

8. The compound of claim 7, wherein R_2 is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acyloxy, acylamino, aryl

substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which are substituted with carboxy or

alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, aryloxy, arylmethyloxy, acylamino, hydroxy, and halogen,

heteroaryl

substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido,

sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

and C_{3-7} cycloalkyl

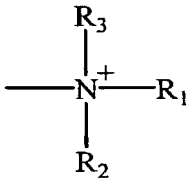
substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

9. The compound of claim 8, wherein R_2 is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

10. The compound of claim 9, wherein R_2 is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl, substituted with one or more groups independently selected from the group consisting of carboxy and alkyloxycarbonyl.

11. The compound according to claim 1, wherein Z is



12. The compound according to claim 11, wherein (l + n) is 2, 3, or 4.

13. The compound according to claim 12, wherein (l + n) is 2, or 3.

14. The compound according to claim 13, wherein X is O.

15. The compound according to claim 14, wherein R10 is hydrogen.

16. The compound according to claim 15, wherein R_3 is C_{1-8} alkyl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, and carboxy.

17. The compound according to claim 6, wherein Ar is

aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

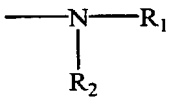
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

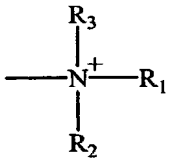
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl,

sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

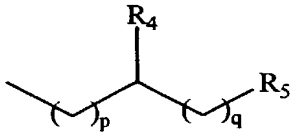
Z is:



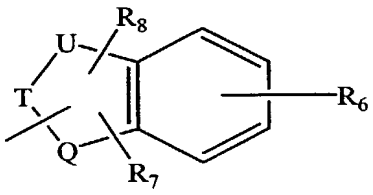
or



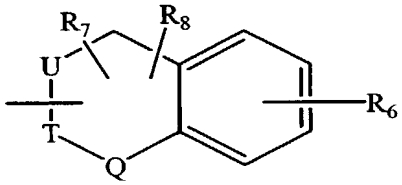
wherein R_1 is:



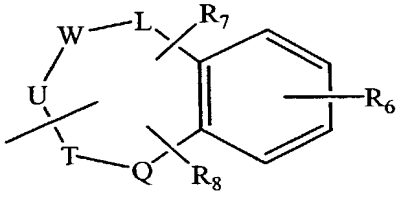
or



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 is selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl,

isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido,

arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

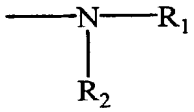
C_{3-7} cycloalkyl

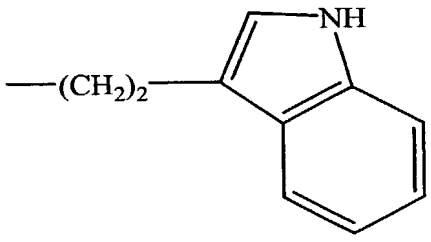
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

further provided that Ar is not 2-hydroxy-5-methoxyphenyl, and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not .

18. The compound according to claim 17, wherein Ar is

aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano,

nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino.

19. The compound according to claim 1, wherein X is S.

20. The compound according to claim 19, wherein R10 is hydrogen.

21. The compound according to claim 20, wherein Ar is

aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide,

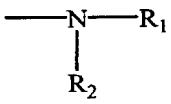
arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Z is:



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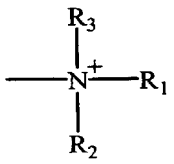
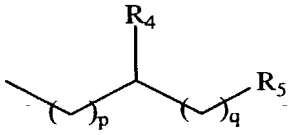


wherein R_1 is:



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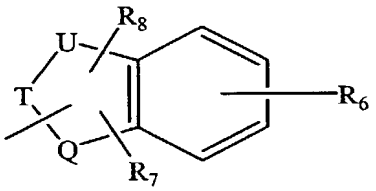

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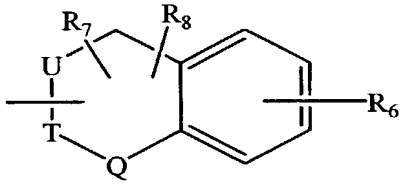

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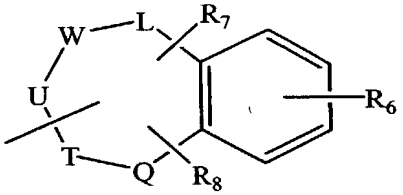


p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 is selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

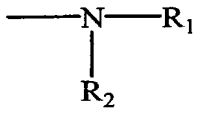
C_{3-7} cycloalkyl

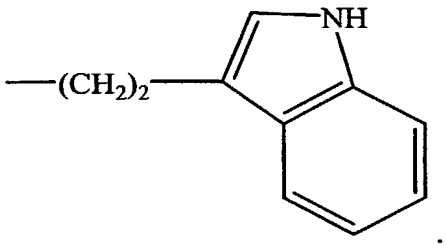
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

further provided that Ar is not 2-hydroxy-5-methoxyphenyl, and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not .

22. The compound according to claim 1, wherein R10 is selected from the group consisting of hydroxy, C_{3-7}cycloalkyloxy, acyloxy, carboxy, carbamoyl, acyl, amino, alkylamino, arylamino, acylamino, C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl, alkyloxycarbonyl,

Wherein the C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl or alkyloxycarbonyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, acyloxy, C_{1-5}alkoxy, aryloxy, heteroaryloxy, nitro, amino, acylamino, alkylamino, arylamino, cyano, aryl, heteroaryl

Wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-5}alkyl or C_{1-5}alkoxy, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydroxy, and halogen;

Ar is aryl or heteroaryl

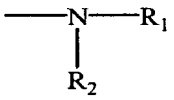
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Z is:



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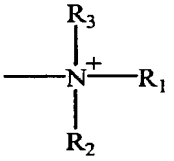
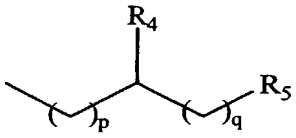


wherein R_1 is:



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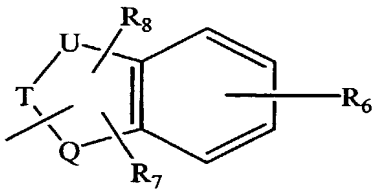

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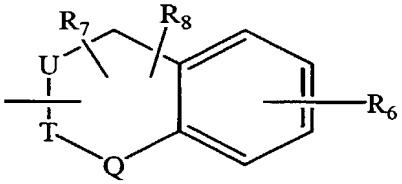

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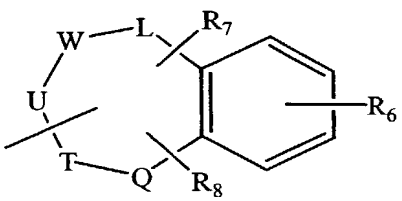


p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 is selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl,

arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide,

arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio,

acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

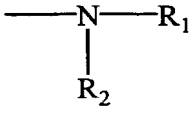
C_{3-7} cycloalkyl

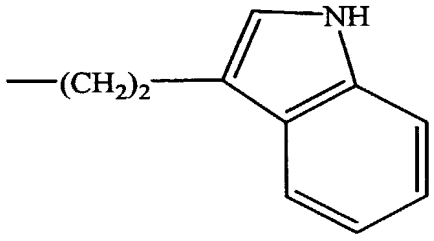
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

further provided that Ar is not 2-hydroxy-5-methoxyphenyl, and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not .

23. The compound according to claim 1 selected from the group consisting of:

N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane;

N-(4-Nitrophenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane;

N-(4-Bromophenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane;

N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-propyl-1,3-diaminopropane;

Methyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino] butylate;

Methyl 4-[[3-(4-bromophenylureido)propyl][(1*R*)-1-phenylethyl]amino]butylate;

Methyl 4-[[3-(4-bromophenylureido)propyl][2-(4-chlorophenyl)ethyl]amino] butylate;

Methyl 4-[[4-(4-bromophenylureido)butyl](1,2,3,4-tetrahydro-1-naphthyl)amino] butylate;

Methyl 4-[[5-(4-bromophenylureido)pentyl](1,2,3,4-tetrahydro-1-naphthyl)amino] butylate;

Methyl 4-[[3-(4-methylphenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino] butylate;

Methyl 4-[[3-(3,4-dichlorophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino] butylate;

4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino] butanoic acid;

4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-phenylethyl]amino] butanoic acid;

4-[[4-(4-Bromophenylureido)butyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[5-(4-Bromophenylureido)pentyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-(4-Methylphenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-(3,4-Dichlorophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl]diethylammonium iodide;

[3-(4-Bromophenylureido)propyl][2-(4-chlorophenyl)ethyl]diethylammonium iodide;

N-Phenylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-2-hydroxy-1,3-diaminopropane;

4-[[3-(4-Chlorophenylthioureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[(3*S*)-3-(4-Bromophenylureido)-3-(tert-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-(4-Bromophenylureido)-2-hydroxypropyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-(4-Chlorophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic;

Methyl 4-[[3-(4-bromophenylureido)propyl](1-indanyl)amino]butylate;

4-[[3-(4-Bromophenylureido)propyl](1-indanyl)amino]butanoic acid;

Methyl 4-[[3-(4-bromophenylureido)propyl][(1*R*)-1-indanyl]amino]butylate;

4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-indanyl]amino]butanoic acid;

Methyl 4-[[3-(4-bromophenylureido)propyl][(1*R*)-1,2,3,4-tetrahydro-1-naphthyl]amino]butylate;

4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1,2,3,4-tetrahydro-1-naphthyl]amino]butanoic acid;

Ethyl 4-[[3-(4-bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate;

4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanamide;

3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[(phenylsulfonyl)carbamoyl]propane;

4-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-butanol;

3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-[1-(triphenylmethyl)tetrazol-5-yl]propane;

3-[[3-(4-Bromophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]-1-(1*H*-tetrazol-5-yl)propane;

Methyl 4-[[3-[4-(carboxy)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate;

4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-(4-methoxyphenyl)ethyl]amino]butanoic acid;

4-[[3-[4-(Ethoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-(4-Iodophenylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-[4-(Butoxycarbonyl)phenylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

[3-(Phenylureido)propyl]bis[2-(4-chlorophenyl)ethyl]amine;

4-[[3-(4-Bromophenylureido)propyl][(1*R*)-1-(4-bromophenyl)ethyl]amino]butanoic acid;

4-[[3-(4-Bromophenylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butanoic acid;

4-[[3-(4-Bromophenylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid;

Methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(tert-butoxycarbonyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate;

Methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate;

Methyl 4-[[(3*S*)-3-(4-bromophenylureido)-3-(benzylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate;

4-[[(3*S*)-3-(4-Bromophenylureido)-3-(isopropylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[(3*S*)-3-(4-Bromophenylureido)-3-(benzylcarbamoyl)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid;

4-[[3-(4-Bromophenylthioureido)propyl][(1*R*)-1-indanyl]amino]butanoic acid;

4-[[3-(4-Bromophenylthioureido)propyl][(1*R*)-1,2,3,4-tetrahydro-1-naphthyl]amino]butanoic acid;

4-[[3-(4-Bromophenylureido)propyl][(1*S*)-1-(4-bromophenyl)ethyl]amino]butanoic acid;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl]bis(4-methylbenzyl)ammonium iodide;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](4-chlorobenzyl)ethylammonium iodide;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](benzyl)ethylammonium iodide;

[3-(Phenylureido)propyl][2-(3-chlorophenyl)ethyl]diethylammonium iodide;

[3-(4-Bromophenylureido)propyl][(1*S*)-1-phenylethyl][3-(carboxy)propyl]ethylammonium trifluoroacetate;

[3-(4-Bromophenylureido)propyl][(1*R*)-1-phenylethyl][3-(carboxy)propyl]ethylammonium trifluoroacetate;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(methoxycarbonyl)butyl] ethylammonium iodide;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl][4-(carboxy)benzyl]ethylammonium iodide;

[5-(Phenylureido)pentyl][2-(4-chlorophenyl)ethyl]diethylammonium iodide;

[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](2-chlorobenzyl)ethylammonium iodide;

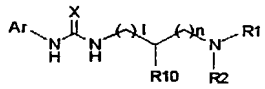
[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](2,5-difluorobenzyl)ethylammonium iodide;

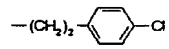
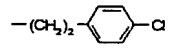
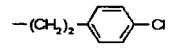
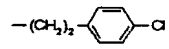
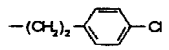
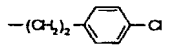
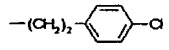
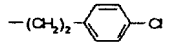
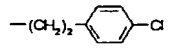
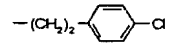
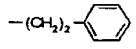
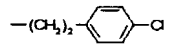
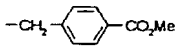
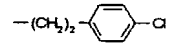
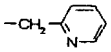
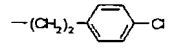
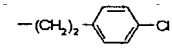
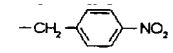
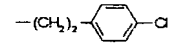
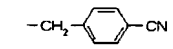
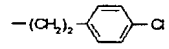
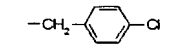
[3-(Phenylureido)propyl][2-(4-chlorophenyl)ethyl](3-fluorobenzyl)ethylammonium iodide;

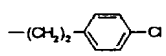
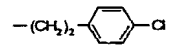
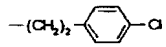
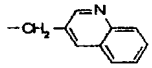
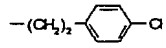
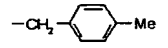
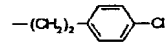
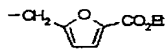
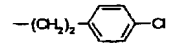
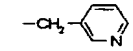
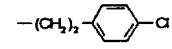
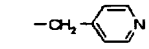
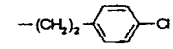
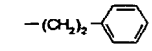
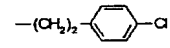
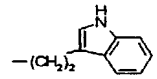
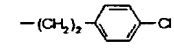
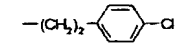
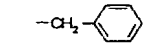
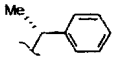
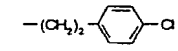
[3-(4-Cyanophenylureido)propyl][2-(3-chlorophenyl)ethyl][2-(2-methoxyehtoxy)ethyl] ethylammonium iodide; and

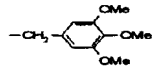
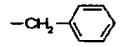
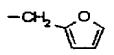
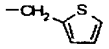
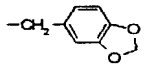
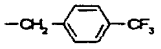
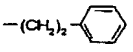
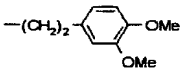
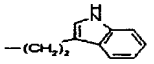
[3-(4-Methoxyphenylureido)propyl][2-(3-chlorophenyl)ethyl][2-(2-methoxyehtoxy)ethyl] ethylammonium iodide.

24. The compound according to claim 1, wherein the compound is defined below:



CPD No.	Ar	X	l	n	R1	R2	R10
1	phenyl	O	1	1		ethyl	H
2	4-nitrophenyl	O	1	1		ethyl	H
3	4-bromophenyl	O	1	1		ethyl	H
4	4-nitrophenyl	O	1	0		ethyl	H
5	4-nitrophenyl	O	1	2		ethyl	H
6	4-chlorophenyl	O	1	1		ethyl	H
7	phenyl	O	1	2		ethyl	H
8	phenyl	O	1	3		ethyl	H
9	2-methoxy-phenyl	O	1	1		ethyl	H
10	phenyl	O	1	1		n-propyl	H
11	phenyl	O	1	1		ethyl	H
12	phenyl	O	1	1			H
13	phenyl	O	1	1			H
14	phenyl	O	1	1		n-butyl	H
15	phenyl	O	1	1			H
16	phenyl	O	1	1			H
17	phenyl	O	1	1			H

18	phenyl	O	1	1			H
19	phenyl	O	1	1			H
20	phenyl	O	1	1			H
21	phenyl	O	1	1			H
22	phenyl	O	1	1			H
23	phenyl	O	1	1			H
24	phenyl	O	1	1			H
25	phenyl	O	1	1			H
26	phenyl	O	1	1			H
27	phenyl	O	1	1		methyl	H
28	phenyl	O	1	1			H
29	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
30	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
31	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
32	4-bromophenyl	O	1	2		$-(CH_2)_3CO_2Me$	H
33	4-bromophenyl	O	1	3		$-(CH_2)_3CO_2Me$	H
34	4-methylphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
35	3,4-dichloro-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H

36	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
37	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
38	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
39	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
40	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
41	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
42	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
43	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
44	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
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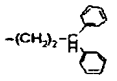
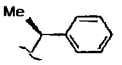
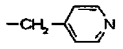
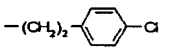
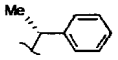
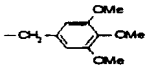
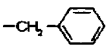
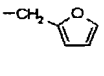
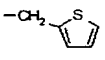
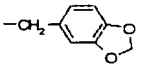
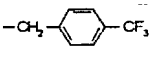
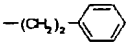
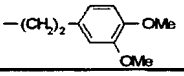
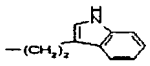
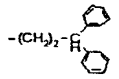
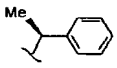
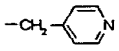
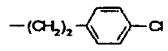
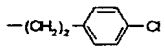
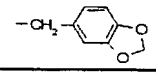
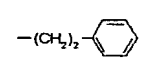
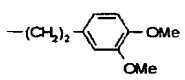
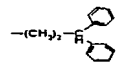
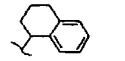
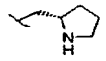
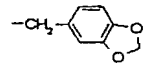
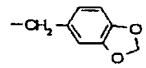
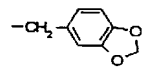
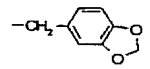
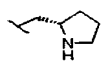
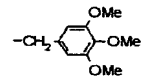
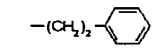
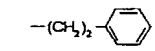
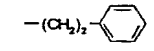
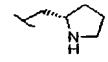
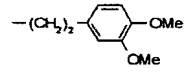
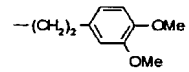
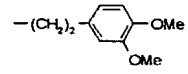
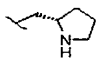
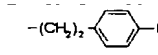
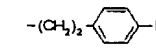
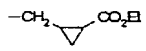
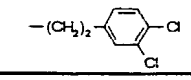
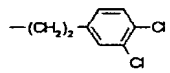
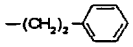
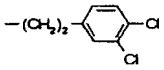
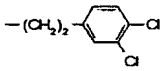
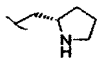
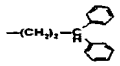
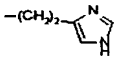
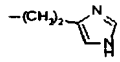
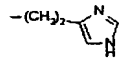
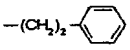
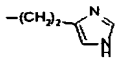
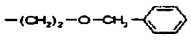
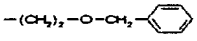
46	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
47	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
48	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
49	phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
50	4-bromophenyl	O	1	0		$-(CH_2)_3CO_2Me$	H
51	3-chlorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
52	3-methylphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
53	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
54	2-biphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H

55	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
56	phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
57	4-methoxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
58	4-phenoxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
59	1-naphthyl	O	1	1		$-(CH_2)_3CO_2Me$	H
60	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
61	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
62	4-bromophenyl	O	1	2		$-(CH_2)_3CO_2H$	H
63	4-bromophenyl	O	1	3		$-(CH_2)_3CO_2H$	H
64	4-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
65	3,4-dichloro-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
66	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
67	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
68	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
69	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
70	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
71	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
72	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
73	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H

74	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
75	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
76	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
77	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
78	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
79	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
80	phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
81	4-bromophenyl	O	1	0		$-(CH_2)_3CO_2H$	H
82	3-chlorophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
83	3-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
84	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
85	2-biphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
86	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
87	phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
88	4-methoxyphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
89	4-phenoxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
90	1-naphthyl	O	1	1		$-(CH_2)_3CO_2H$	H
93	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		ethyl	H
94	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3SMe$	H

95	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
96	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
97	4-chloro-3-(trifluoro-methyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
98	2-biphenyl	O	1	1			H
99	2-biphenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H
100	2-biphenyl	O	1	1		$-(CH_2)_3SMe$	H
101	2-biphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
102	2-biphenyl	O	1	1			H
103	2-biphenyl	O	1	1		$-(CH_2)_3SMe$	H
104	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
105	2-biphenyl	O	1	1		$-(CH_2)_3SMe$	H
106	2-biphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
107	2-biphenyl	O	1	1			H
108	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
109	2-biphenyl	O	1	1			H
110	2-biphenyl	O	1	1			H
111	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
112	2-biphenyl	O	1	1			H
113	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H

114	2-biphenyl	O	1	1			H
115	2-biphenyl	O	1	1			H
116	2-biphenyl	O	1	1			H
117	2-biphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
118	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
119	4-bromophenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H
120	4-bromophenyl	O	1	1			H
121	4-bromophenyl	O	1	1			H
122	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
123	4-bromophenyl	O	1	1			H
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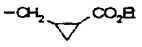
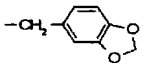
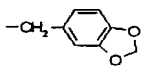
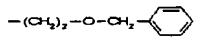
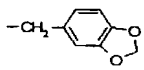
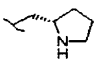
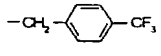
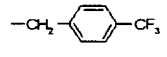
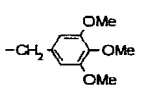
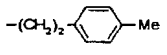
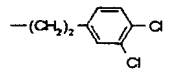
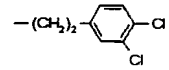
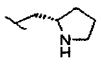
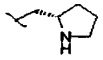
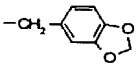
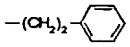
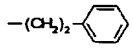
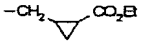
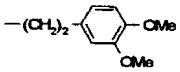
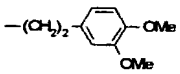
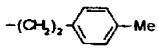
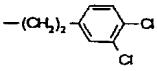
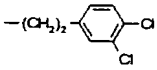
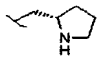
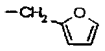
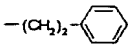
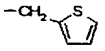
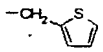
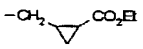
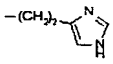
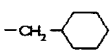
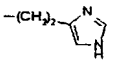
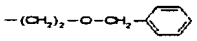
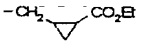
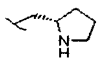
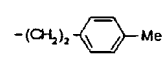
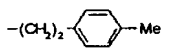
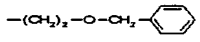
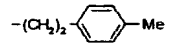
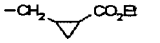
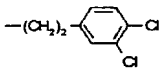
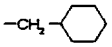
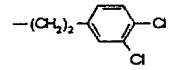
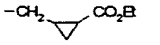
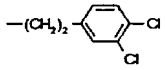
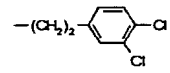
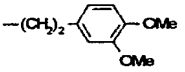
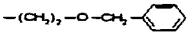
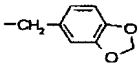
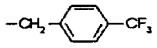
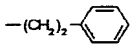
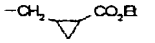
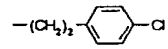
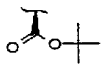
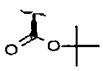
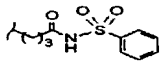
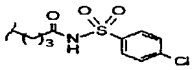
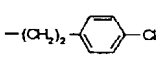
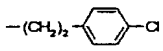
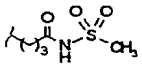
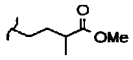
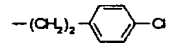
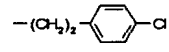
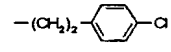
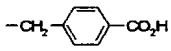
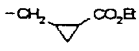
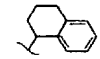
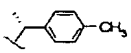
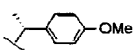
125	4-bromophenyl	O	1	1			H
126	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
127	4-bromophenyl	O	1	1			H
128	4-bromophenyl	O	1	1			H
129	4-bromophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
130	4-bromophenyl	O	1	1		$-(CH_2)_3SMe$	H
131	4-bromophenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H
132	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H

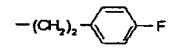
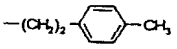
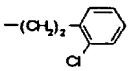
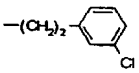
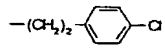
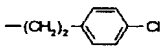
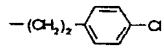
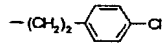
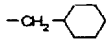
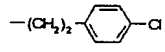
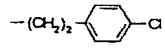
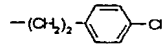
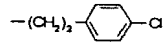
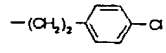
133	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
134	4-bromophenyl	O	1	1			H
135	3-methylphenyl	O	1	1			H
136	3-methylphenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
137	3-methylphenyl	O	1	1		ethyl	H
138	3-methylphenyl	O	1	1			H
139	3-methylphenyl	O	1	1		$-(CH_2)_3SMe$	H
140	3-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
141	3-methylphenyl	O	1	1		$-(CH_2)_3SMe$	H
142	3-methylphenyl	O	1	1		$-(CH_2)_3SMe$	H
143	3-methylphenyl	O	1	1			H
144	3-chlorophenyl	O	1	1			H
145	3-chlorophenyl	O	1	1		$-(CH_2)_2CH(CH_3)_2$	H
146	3-chlorophenyl	O	1	1			H
147	3-chlorophenyl	O	1	1			H
148	3-chlorophenyl	O	1	1			H
149	3-chlorophenyl	O	1	1			H
150	3-chlorophenyl	O	1	1			H
151	3-chlorophenyl	O	1	1		$-CH_2CH(CH_3)_2$	H

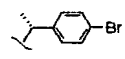
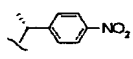
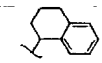
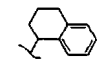
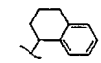
152	3-chlorophenyl	O	1	1			H
153	3-chlorophenyl	O	1	1			H
154	3-chlorophenyl	O	1	1			H
155	3-chlorophenyl	O	1	1			H
156	3-chlorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
157	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3SMe$	H
158	2,4-dimethoxy-phenyl	O	1	1		$-(CH_2)_3SMe$	H
159	4-methoxy-phenyl	O	1	1			H
160	3,4-dichloro-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
161	1-naphthyl	O	1	1		$-(CH_2)_3CO_2H$	H
162	1-naphthyl	O	1	1			H
163	phenyl	O	1	1		ethyl	OH
164	4-chlorophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
165	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$	
166	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$	
167	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	OH
168	4-methoxy-phenyl	S	1	1		$-(CH_2)_3CO_2H$	H
169	4-benzyloxy-phenyl	S	1	1		$-(CH_2)_3CO_2H$	H
170	4-(trifluoro-methoxy)phenyl	S	1	1		$-(CH_2)_3CO_2H$	H

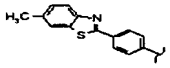
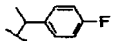
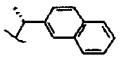
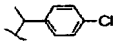
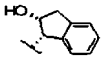
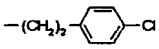
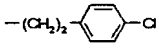
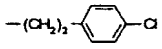
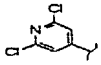
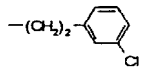
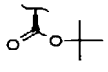
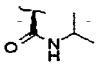
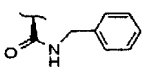
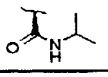
171	4-chlorophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
172	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
173	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
174	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
175	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
176	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
177	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
178	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
179	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
180	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
181	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
182	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
183	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
184	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Et$	H
185	4-chlorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
186	4-bromophenyl	O	1	1		$-CH_2CO_2H$	H
187	4-fluorophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
188	4-fluorophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
189	2-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H

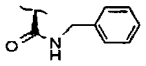
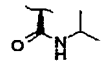
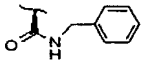
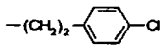
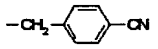
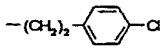
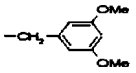
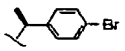
190	2-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
191	4-bromophenyl	O	1	1		ethyl	H
192	phenyl	O	1	1		ethyl	H
193	4-bromophenyl	O	1	1		$-(CH_2)_3CONH_2$	H
194	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
195	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
196	4-bromophenyl	O	1	1			H
197	4-bromophenyl	O	1	1			H
198	3-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
199	3-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
200	4-bromo-2-methylphenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
201	4-bromo-2-methylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
202	4-bromophenyl	O	1	1		$-(CH_2)_4OCOCH_3$	H
203	4-bromophenyl	O	1	1		$-(CH_2)_4OH$	H
204	4-bromophenyl	O	1	1		$-(CH_2)_5OCOCH_3$	H
205	4-bromophenyl	O	1	1		$-(CH_2)_5OH$	H
206	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
207	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
208	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2Me$	H

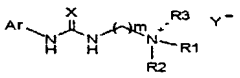
209	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
210	4-bromophenyl	O	1	1			H
211	4-bromophenyl	O	1	1		$-(CH_2)_5CO_2H$	H
212	4-bromophenyl	O	1	1			H
213	4-bromophenyl	O	1	1		$-(CH_2)_4CO_2Me$	H
214	4-bromophenyl	O	1	1		$-(CH_2)_4CO_2H$	H
215	4-bromophenyl	O	1	1		$-(CH_2)_3OCOCH_3$	H
216	4-bromophenyl	O	1	1		$-(CH_2)_3OH$	H
217	4-bromophenyl	O	1	1			H
218	4-bromophenyl	O	1	1			H
219	phenyl	O	1	1		$-(CH_2)_3OH$	H
220	phenyl	O	1	1		$-CH_2CONH_2$	H
221	phenyl	O	1	1		$-CH_2CH=CH_2$	H
222	4-bromophenyl	O	1	1			H
223	4-bromophenyl	O	1	1			H
224	4-bromophenyl	O	1	1			H
225	4-carboxy-phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
226	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
227	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H

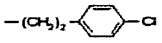
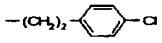
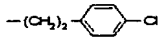
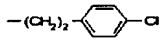
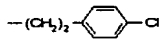
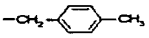
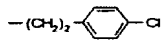
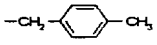
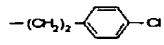
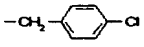
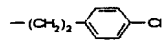
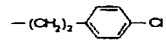
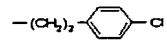
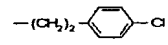
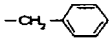
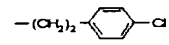
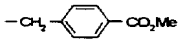
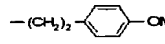
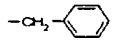
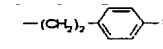
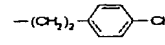
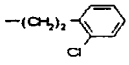
228	4-(ethoxy-carbonyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
229	4-iodophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
230	phenyl	O	1	1		ethyl	H
231	phenyl	O	1	1		ethyl	H
232	phenyl	O	1	1		ethyl	H
233	phenyl	O	1	1		ethyl	H
234	phenyl	O	1	1		ethyl	H
235	4-carboxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
236	3-(ethoxy-carbonyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
237	4-(n-butyloxy-carbonyl)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
238	phenyl	O	1	1			H
239	phenyl	O	1	1		$-CH_2CH(CH_3)_2$	H
240	phenyl	O	1	1			H
241	phenyl	O	1	1		$-(CH_2)_4CO_2Me$	H
242	phenyl	O	1	1		$-(CH_2)_5CO_2Et$	H
243	phenyl	O	1	1		$-(CH_2)_2CONH_2$	H
244	phenyl	O	1	1		$-(CH_2)_2OCOCH_3$	H
245	phenyl	O	1	1		$-CH_2CO_2Me$	H
246	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H

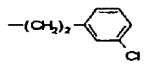
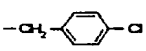
247	3-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
248	3-chlorophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
249	4-iodophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
250	4-methylphenyl	S	1	1		$-(CH_2)_3CO_2H$	H
251	3,4-dichloro-phenyl	S	1	1		$-(CH_2)_3CO_2H$	H
252	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H
253	3-bromophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H
254	3-chlorophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H
255	4-iodophenyl	S	1	1		$-(CH_2)_3CO_2Me$	H
256	3,4-dichloro-phenyl	S	1	1		$-(CH_2)_3CO_2Me$	H
257	4-fluorophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
258	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
259	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
260	3-cyanophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
261	3-methoxy-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
262	3-acetylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
263	3-(methylthio) phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
264	4-methylthio-phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
265	2-naphthyl	O	1	1		$-(CH_2)_3CO_2H$	H

266	4-(trifluoro-methoxy)phenyl	O	1	1		$-(CH_2)_3CO_2H$	H
267		O	1	1		$-(CH_2)_3CO_2H$	H
268	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
269	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
270	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
271	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
272	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
273	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H
274	phenyl	O	1	1		$-(CH_2)_3CO_2Me$	H
275	phenyl	O	1	1		$-(CH_2)_2OCH_3$	H
276	phenyl	O	1	1		$-CH(CH_3)_2$	H
277	4-biphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
278	4-acetylphenyl	O	1	1		$-(CH_2)_3CO_2H$	H
279		O	1	1		$-(CH_2)_3CO_2H$	H
280	phenyl	O	1	1			H
281	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2Me$	
282	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2Me$	
283	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2Me$	
284	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$	

285	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$	
286	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$	
287	4-bromophenyl	O	0	2		$-(CH_2)_3CO_2H$	
288	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
289	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
290	4-bromophenyl	S	1	1		$-(CH_2)_3CO_2H$	H
291	phenyl	O	1	1			H
292	phenyl	O	1	1			H
293	4-bromophenyl	O	1	1		$-(CH_2)_3CO_2H$	H



CPD No.	Ar	X	m	R1	R2	R3	Y
91	phenyl	O	3		ethyl	ethyl	I
92	4-bromo-phenyl	O	3		ethyl	ethyl	I
294	4-bromo-phenyl	O	3		n-butyl	ethyl	I
295	4-bromo-phenyl	O	3		n-propyl	ethyl	I
296	phenyl	O	3				Br
297	phenyl	O	3			ethyl	I
298	phenyl	O	3			ethyl	I
299	phenyl	O	3		$-(CH_2)_3OH$	ethyl	I
300	phenyl	O	3		$-CH_2CONH_2$	ethyl	I
301	phenyl	O	3		$-CH_2CH=CH_2$	ethyl	I
302	phenyl	O	3			ethyl	I
303	phenyl	O	3			ethyl	I
304	phenyl	O	3		ethyl	ethyl	I
305	phenyl	O	3		ethyl	ethyl	I
306	phenyl	O	3		ethyl	ethyl	I
307	phenyl	O	3		ethyl	ethyl	I
308	phenyl	O	3		ethyl	ethyl	I

309	phenyl	O	3		ethyl	ethyl	I
310	phenyl	O	3		ethyl	ethyl	I
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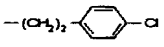
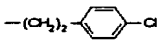
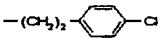
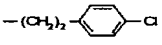
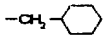
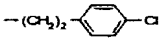
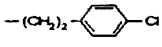
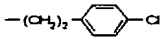
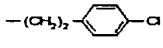
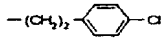
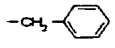
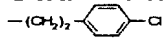
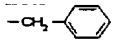
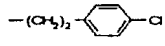
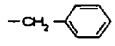
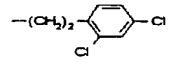
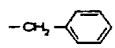
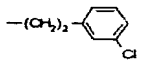
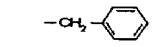
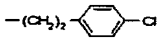
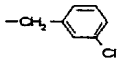
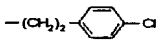
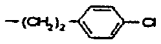
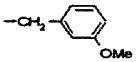
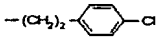
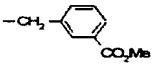
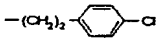
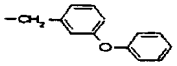
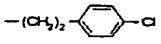
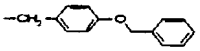
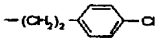
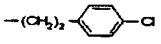
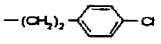
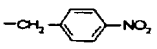
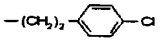
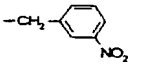
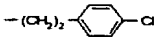
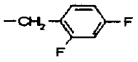
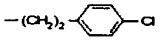
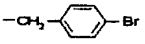
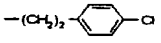
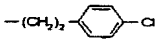
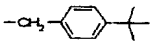
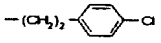
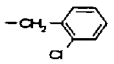
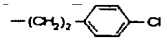
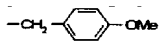
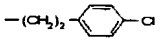
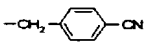
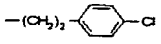
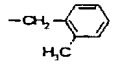
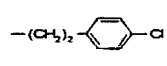
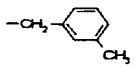
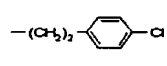
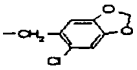
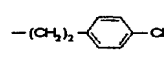
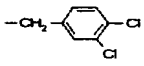
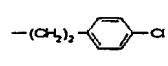
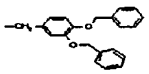
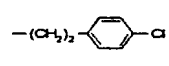
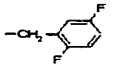
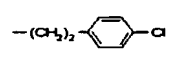
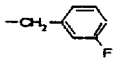
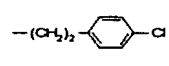
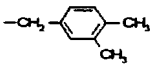
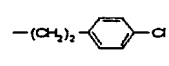
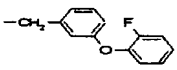
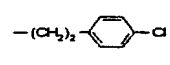
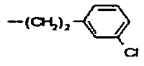
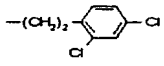
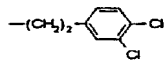
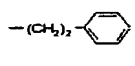
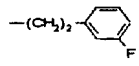
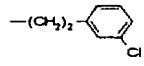
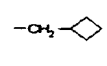
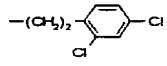
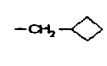
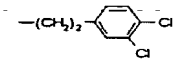
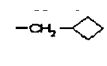
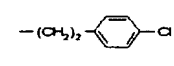
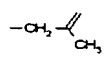
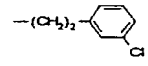
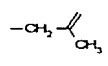
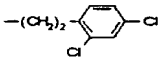
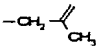
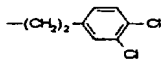
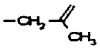
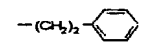
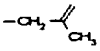
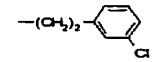
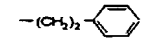
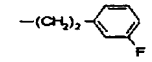
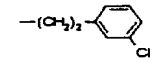
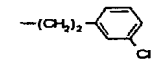
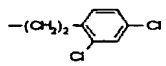
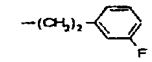
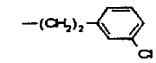
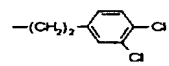
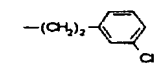
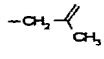
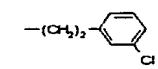
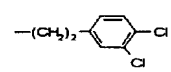
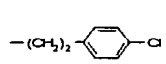
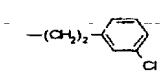
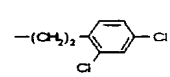
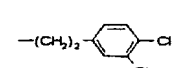
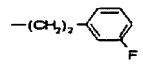
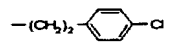
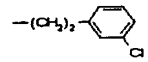
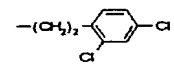
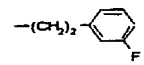
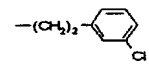
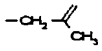
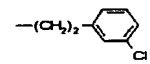
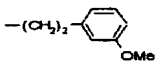
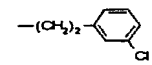
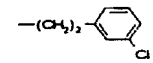
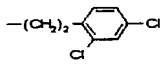
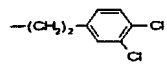
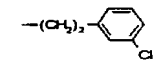
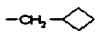
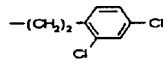
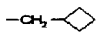
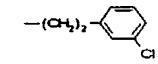
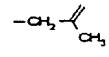
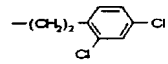
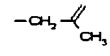
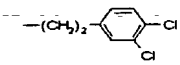
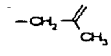
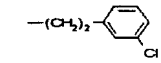
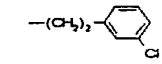
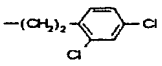
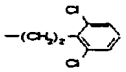
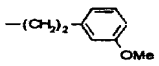
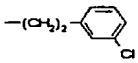
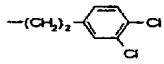
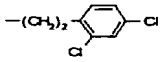
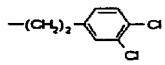
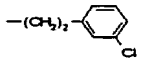
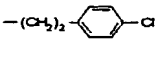
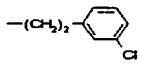
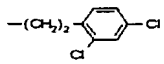
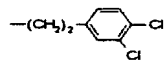
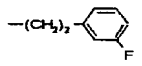
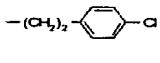
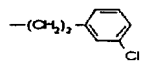
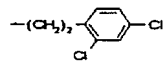
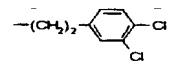
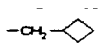
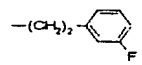
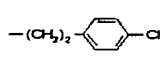
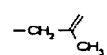
312	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2Me$	ethyl	I
313	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2Me$	ethyl	I
314	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2Me$	ethyl	I
315	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2H$	ethyl	CF_3COO
316	4-bromo-phenyl	O	3		$-(CH_2)_3CO_2H$	ethyl	CF_3COO
317	phenyl	O	3			ethyl	I
318	phenyl	O	3		$-CH_2CH(CH_3)_2$	ethyl	I
319	phenyl	O	3			ethyl	I
320	phenyl	O	3		$-(CH_2)_4CO_2Me$	ethyl	I
321	phenyl	O	3		$-(CH_2)_5CO_2Et$	ethyl	I
322	phenyl	O	3			ethyl	I
323	phenyl	O	5		ethyl	ethyl	I
324	4-methoxy-phenyl	O	3			ethyl	I
325	3,4-dichloro-phenyl	O	3			ethyl	I
326	4-cyano-phenyl	O	3			ethyl	I
327	phenyl	O	3			ethyl	I

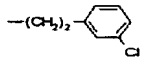
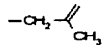
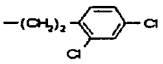
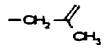
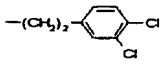
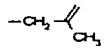
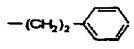
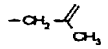
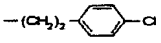
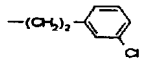
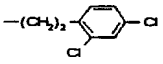
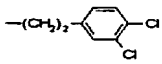
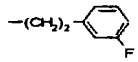
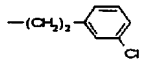
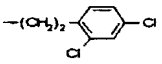
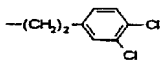
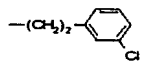
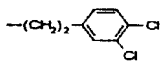
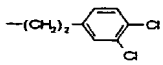
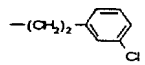
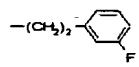
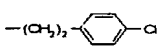
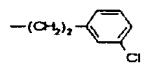
328	phenyl	O	3			ethyl	I
329	phenyl	O	3			ethyl	I
330	phenyl	O	3			ethyl	I
331	phenyl	O	3			ethyl	I
332	phenyl	O	3			ethyl	I
333	phenyl	O	3			ethyl	I
334	phenyl	O	3			ethyl	I
335	4-bromo-phenyl	S	3		ethyl	ethyl	I
336	phenyl	S	3		ethyl	ethyl	I
337	phenyl	O	3			ethyl	I
338	phenyl	O	3			ethyl	I
339	phenyl	O	3			ethyl	I
340	phenyl	O	3			ethyl	I
341	phenyl	O	3			ethyl	I
342	phenyl	O	3			ethyl	I
343	phenyl	O	3			ethyl	I
344	phenyl	O	3			ethyl	I
345	phenyl	O	3			ethyl	I
346	phenyl	O	3			ethyl	I

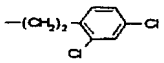
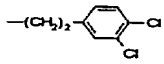
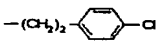
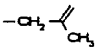
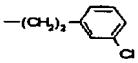
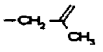
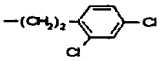
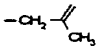
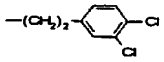
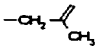
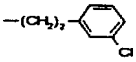
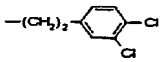
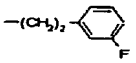
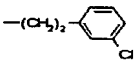
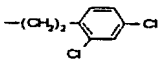
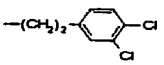
347	phenyl	O	3			ethyl	I
348	phenyl	O	3			ethyl	I
349	phenyl	O	3			ethyl	I
350	phenyl	O	3			ethyl	I
351	phenyl	O	3			ethyl	I
352	phenyl	O	3			ethyl	I
353	phenyl	O	3			ethyl	I
354	phenyl	O	3			ethyl	I
355	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
356	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
357	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
358	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
359	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
360	3,4-dichloro-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
361	3,4-dichloro-phenyl	O	3			ethyl	I
362	3,4-dichloro-phenyl	O	3			ethyl	I
363	3,4-dichloro-phenyl	O	3			ethyl	I
364	3,4-dichloro-phenyl	O	3			ethyl	I
365	3,4-dichloro-phenyl	O	3			ethyl	I

366	3,4-dichloro-phenyl	O	3			ethyl	I
367	3,4-dichloro-phenyl	O	3			ethyl	I
368	3,4-dichloro-phenyl	O	3			ethyl	I
369	3,4-dichloro-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
370	3,4-dichloro-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
371	3,4-dichloro-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
372	4-bromo-phenyl	O	3		$-CH_2CN$	ethyl	I
373	4-bromo-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
374	4-bromo-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
375	4-bromo-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
376	4-bromo-phenyl	O	3			ethyl	I
377	4-bromo-phenyl	O	3			ethyl	I
378	4-bromo-phenyl	O	3			ethyl	I
379	4-bromo-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
380	4-bromo-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
381	4-bromo-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
382	4-bromo-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
383	4-bromo-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
384	4-bromo-phenyl	O	3		$-(CH_2)_2F$	ethyl	I

385	4-bromo-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
386	4-(trifluoro-methyl)phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
387	4-(trifluoro-methyl)phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
388	4-(trifluoro-methyl)phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
389	4-(trifluoro-methyl)phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
390	4-(trifluoro-methyl)phenyl	O	3			ethyl	I
391	4-(trifluoro-methyl)phenyl	O	3		$-(CH_2)_2F$	ethyl	I
392	4-cyano-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
393	4-cyano-phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I
394	4-cyano-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
395	4-cyano-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
396	4-cyano-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
397	4-cyano-phenyl	O	3			ethyl	I
398	4-cyano-phenyl	O	3			ethyl	I
399	4-cyano-phenyl	O	3			ethyl	I
400	4-cyano-phenyl	O	3			ethyl	I
401	4-cyano-phenyl	O	3			ethyl	I
402	4-cyano-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
403	4-cyano-phenyl	O	3		$-(CH_2)_2F$	ethyl	I

404	4-cyano-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
405	4-cyano-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
406	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
407	phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I
408	phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I
409	phenyl	O	3		$-CH_2CONH_2$	ethyl	I
410	phenyl	O	3		$-CH_2CONH_2$	ethyl	I
411	phenyl	O	3		$-CH_2CN$	ethyl	I
412	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
413	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
414	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
415	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
416	phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
417	phenyl	O	3			ethyl	I
418	phenyl	O	3			ethyl	I
419	phenyl	O	3			ethyl	I
420	phenyl	O	3			ethyl	I
421	phenyl	O	3			ethyl	I
422	phenyl	O	3			ethyl	I

423	phenyl	O	3			ethyl	I
424	phenyl	O	3			ethyl	I
425	phenyl	O	3			ethyl	I
426	phenyl	O	3			ethyl	I
427	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
428	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
429	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
430	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
431	phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
432	phenyl	O	3		$-(CH_2)_2F$	ethyl	I
433	phenyl	O	3		$-(CH_2)_2F$	ethyl	I
434	phenyl	O	3		$-(CH_2)_2F$	ethyl	I
435	4-methoxy-phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I
436	4-methoxy-phenyl	O	3		$-(CH_2)_2CH(CH_3)_2$	ethyl	I
437	4-methoxy-phenyl	O	3		$-CH_2CONH_2$	ethyl	I
438	4-methoxy-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
439	4-methoxy-phenyl	O	3		$-(CH_2)_2O(CH_2)_2OMe$	ethyl	I
440	4-methoxy-phenyl	O	3			ethyl	I
441	4-methoxy-phenyl	O	3			ethyl	I

442	4-methoxy-phenyl	O	3			ethyl	I
443	4-methoxy-phenyl	O	3			ethyl	I
444	4-methoxy-phenyl	O	3			ethyl	I
445	4-methoxy-phenyl	O	3			ethyl	I
446	4-methoxy-phenyl	O	3			ethyl	I
447	4-methoxy-phenyl	O	3			ethyl	I
448	4-methoxy-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
449	4-methoxy-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
450	4-methoxy-phenyl	O	3		$-CH_2CH(CH_2CH_3)_2$	ethyl	I
451	4-methoxy-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
452	4-methoxy-phenyl	O	3		$-(CH_2)_2F$	ethyl	I
453	4-methoxy-phenyl	O	3		$-(CH_2)_2F$	ethyl	I

25. A pharmaceutical composition comprising a compound according to claim 1.

26. A method of treating CCR-3 mediated diseases in a patient, comprising administering to said patient an effective amount of the pharmaceutical composition of claim 25.

27. The method of claim 26, wherein said CCR-3 mediated disease is an eosinophil mediated allergic disease.

28. The method of claim 27, wherein said eosinophil mediated allergic disease is selected from the group consisting of asthma, rhinitis, eczema, inflammatory bowel diseases and parasitic infections.

29. The method of claim 26, wherein said CCR-3 mediated disease is a T-cell or a dendritic cell mediated disease.

30. The method of claim 29, wherein said T-cell or dendritic cell mediated disease is selected from the group consisting of autoimmune diseases and HIV.

31. The method of claim 26, wherein said pharmaceutical composition comprises a prodrug.

32. A kit for treating CCR-3 mediated diseases in a patient, comprising:

(A) a pharmaceutical composition of claim 25;

(B) reagents to effect administration of said pharmaceutical composition to said patient; and

(C) instruments to effect administration of said pharmaceutical composition to said patient.

33. A method of inhibiting a CCR-3 mediated cellular response in a cell which expresses CCR-3, comprising contacting said cell with a compound according to claim 1, such that said cellular response is inhibited.

34. The method according to claim 33, whereinin the CCR-3 mediated cellular repsonse is a chemotaxis.

35. A method of treating a CCR-3 mediated diseases in a mammal, comprising administering to said mammal an effective amount of the pharmaceutical composition according to claim 25.

36. The use of a compound according to claim 1 in the manufacture of a medicament for treating a CCR-3 mediated disease.

37. The use of claim 36, wherein said CCR-3 mediated disease is an eosinophil-mediated allergic disease.

38. The use of claim 37, wherein said eosinophil-mediated allergic disease is selected from the group consisting of asthma, rhinitis, eczema, inflammatory bowel diseases and parasitic infections.

39. The use of claim 36, wherein said CCR-3 mediated disease is a T-cell or a dendritic cell mediated disease.

40. The use of claim 39, wherein said T-cell or dendritic cell mediated disease is selected from the group consisting of autoimmune diseases and HIV.

41. The use of a composition comprising a compound according to claim 1 and a prodrug in the manufacture of a medicament for treating a CCR-3 mediated disease.

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(26) Publication Language: English

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(74) Agents: **BENT, Stephen, A.** et al.; Foley & Lardner, Suite 500, 3000 K Street N.W., Washington, DC 20007-5109 (US).

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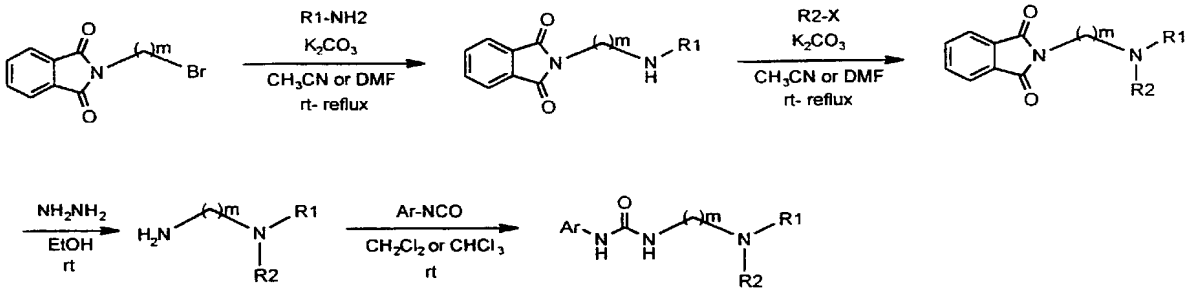
WO 01/09088 A1

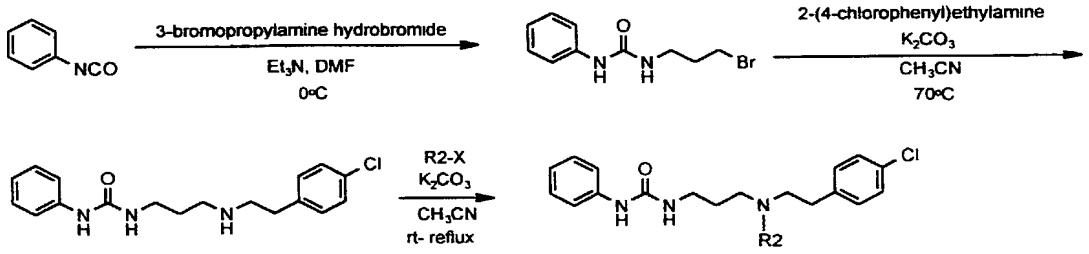
(54) Title: UREA DERIVATIVES AS INHIBITORS OF CCR-3 RECEPTOR

(57) Abstract: Urea and thiourea derivatives inhibit cell function of the chemokine receptor CCR-3. These compounds offer an effective means for treating a range of diseases thought to be mediated by the CCR-3 receptor. A variety of useful urea and thiourea derivatives can be synthesized using liquid and solid phase synthesis protocols.

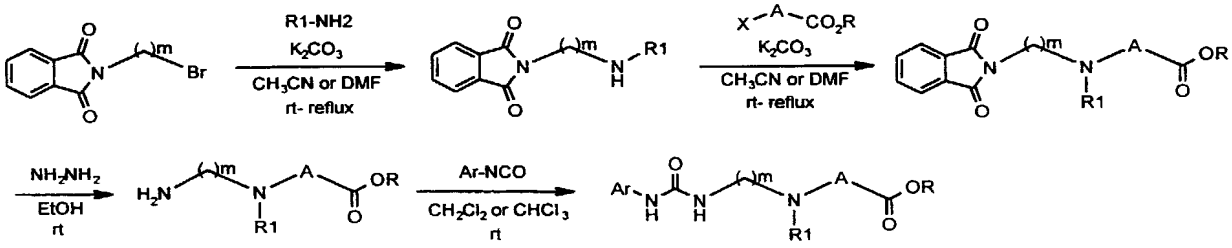
Scheme 1



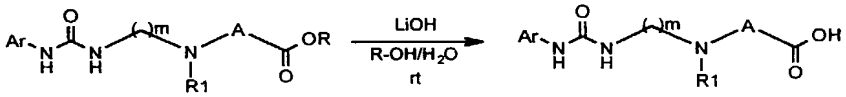
Scheme 2



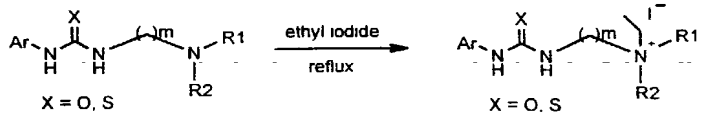
Scheme 3



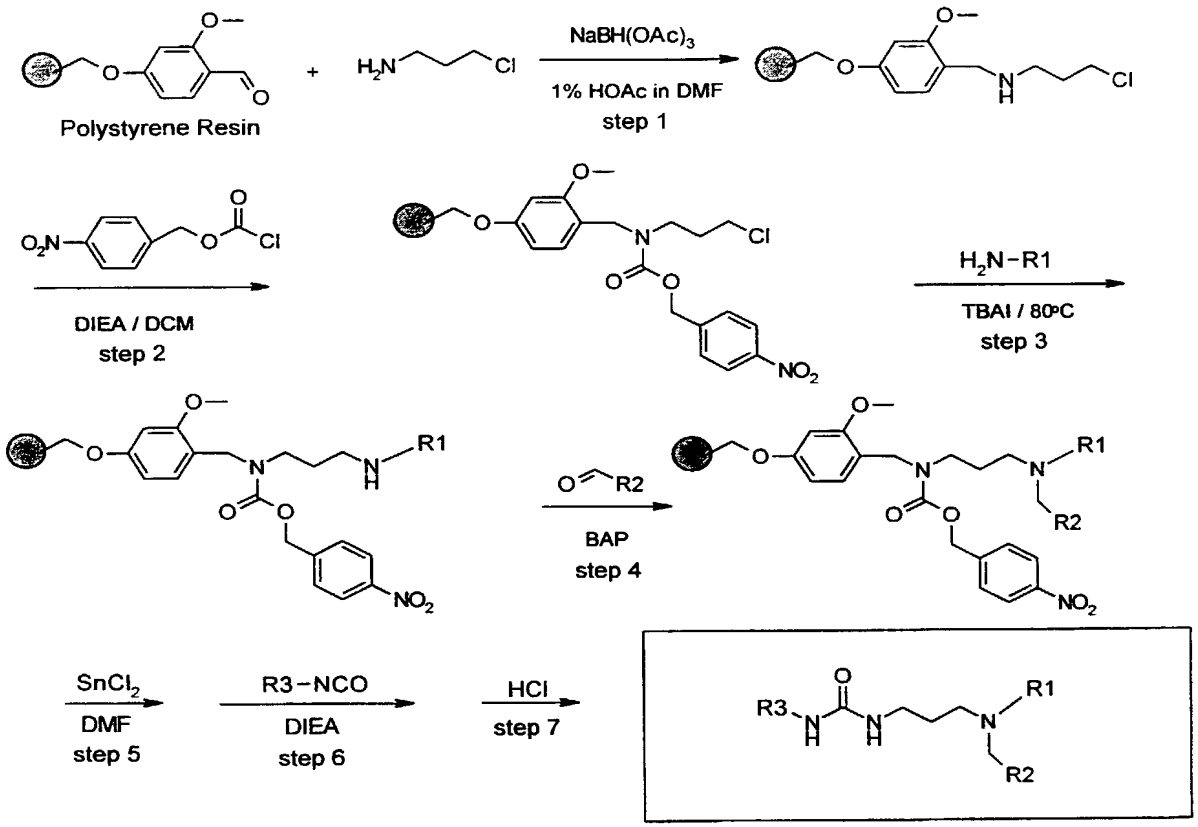
Scheme 4



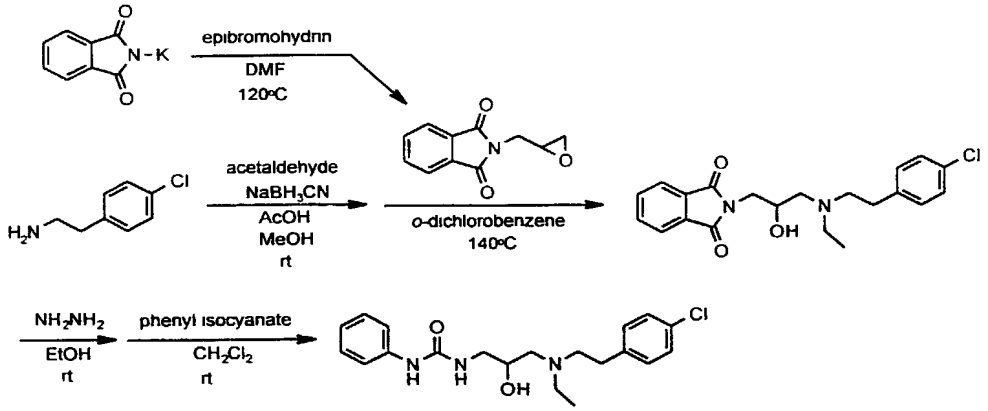
Scheme 5



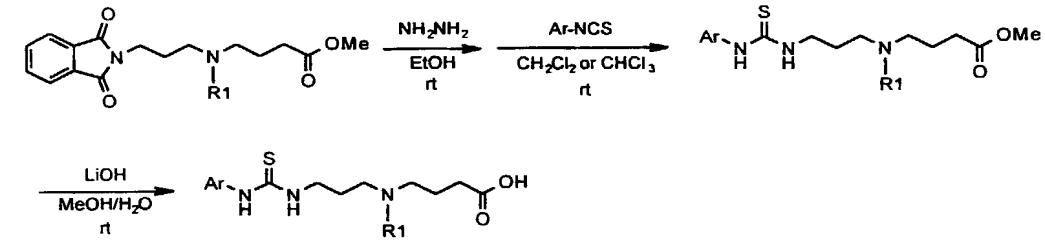
Scheme 6


Polystyrene Resin
NaBH(OAc)3
1% HOAc in DMF
step 1
DIEA / DCM
step 2
H2N-R1
TBAI / 80°C
step 3
BAP
step 4
SnCl2
DMF
step 5
R3-NCO
DIEA
step 6
HCl
step 7

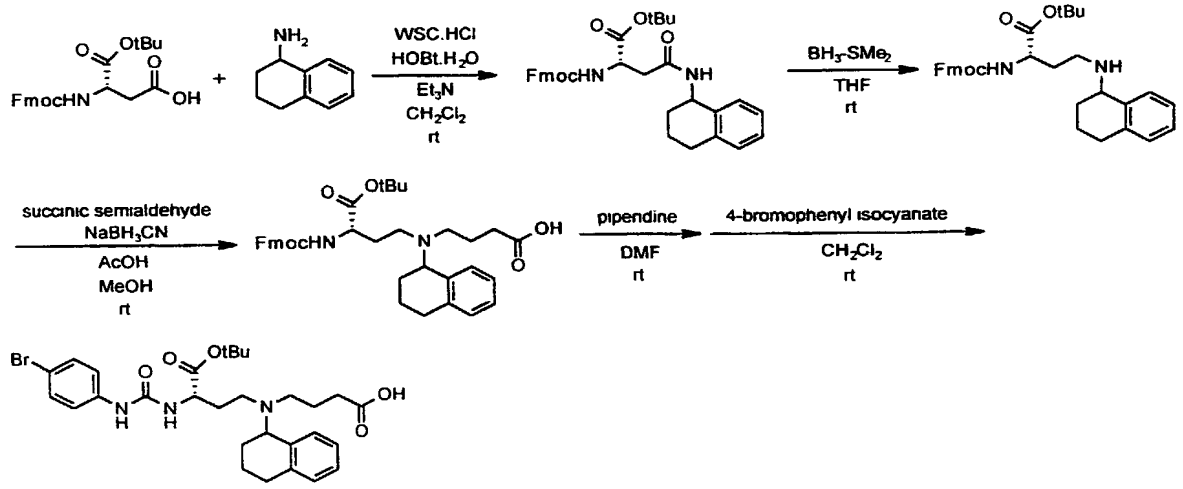
Scheme 7



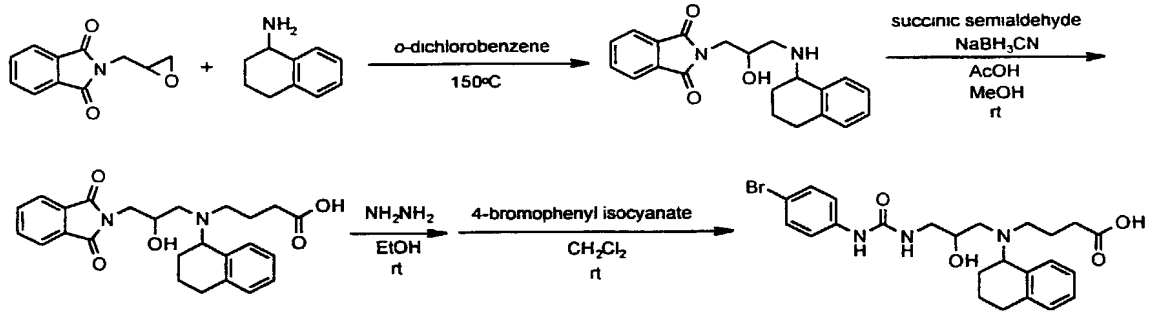
Scheme 8



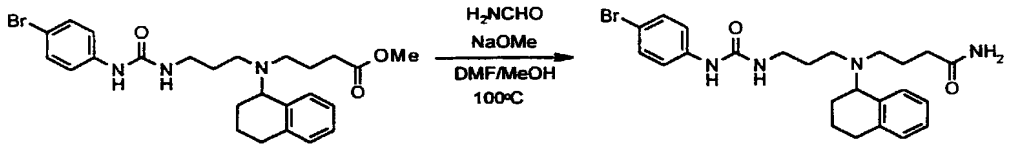
Scheme 9



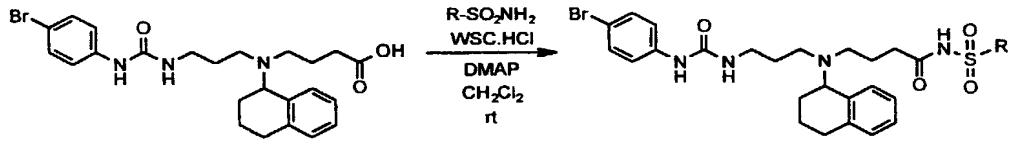
Scheme 10



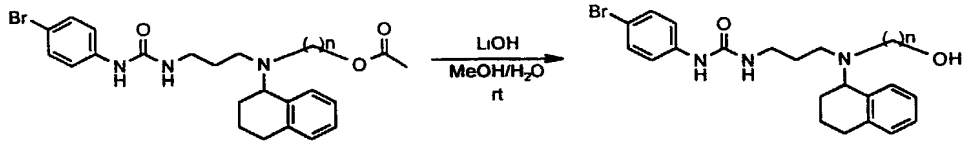
Scheme 11



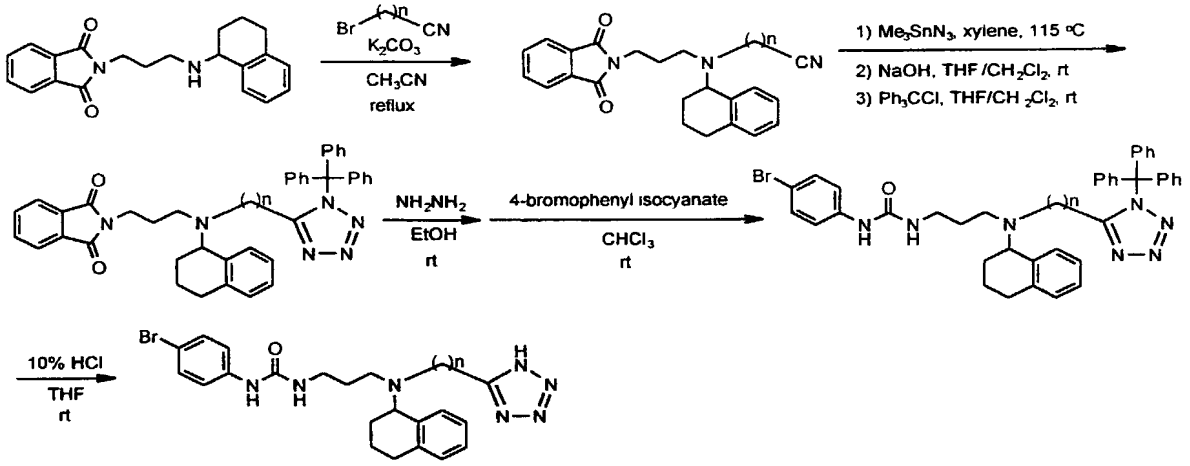
Scheme 12



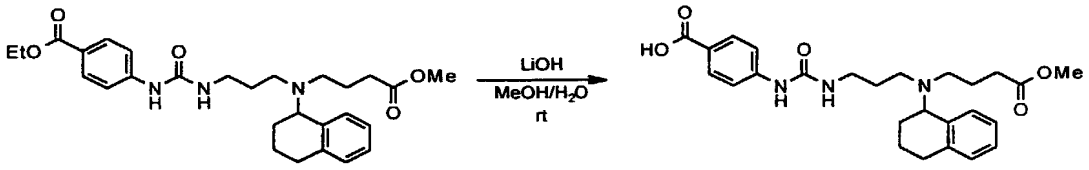
Scheme 13



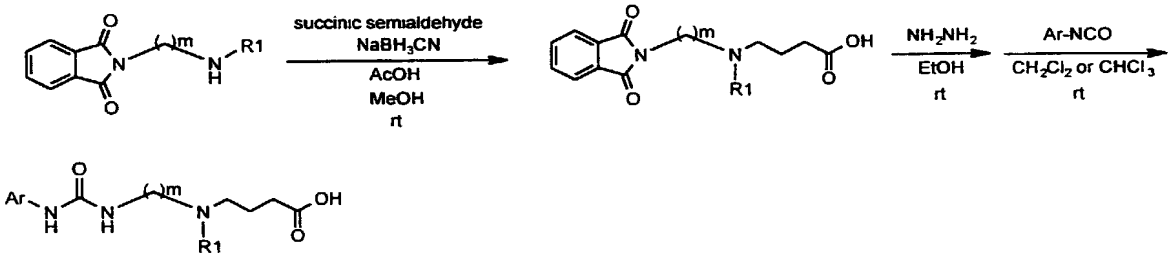
Scheme 14



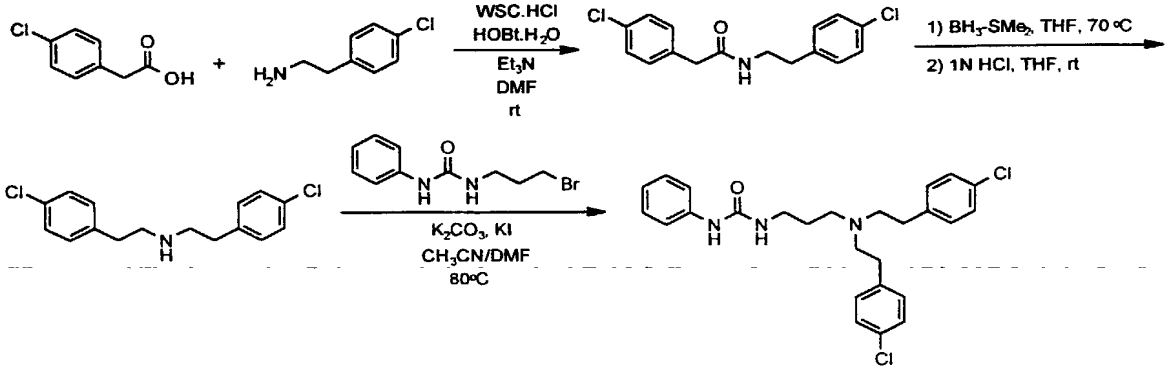
Scheme 15



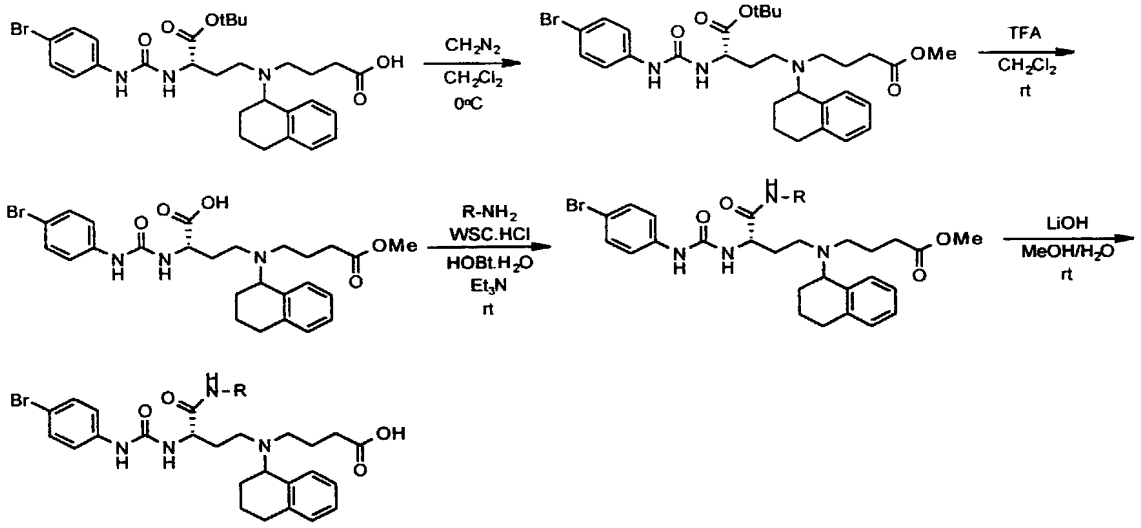
Scheme 16



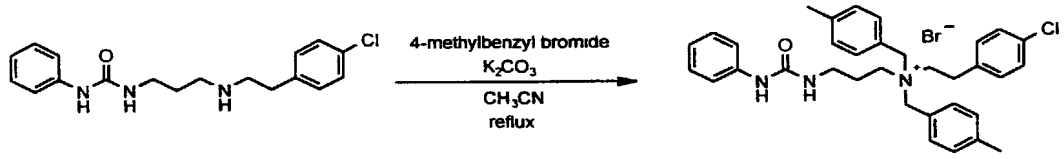
Scheme 17



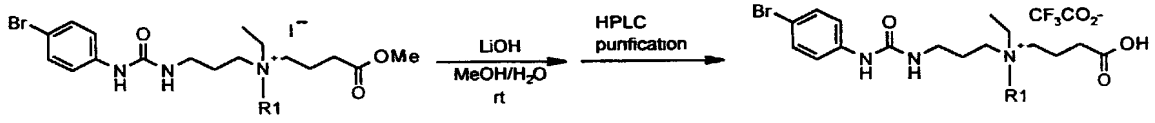
Scheme 18



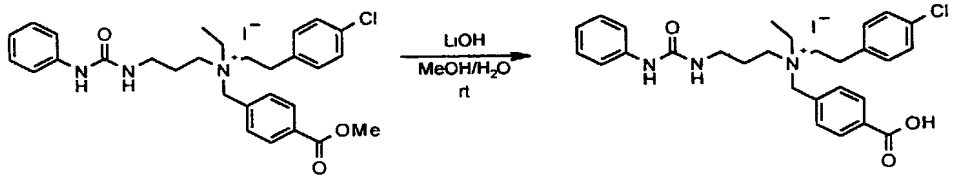
Scheme 19



Scheme 20



Scheme 21



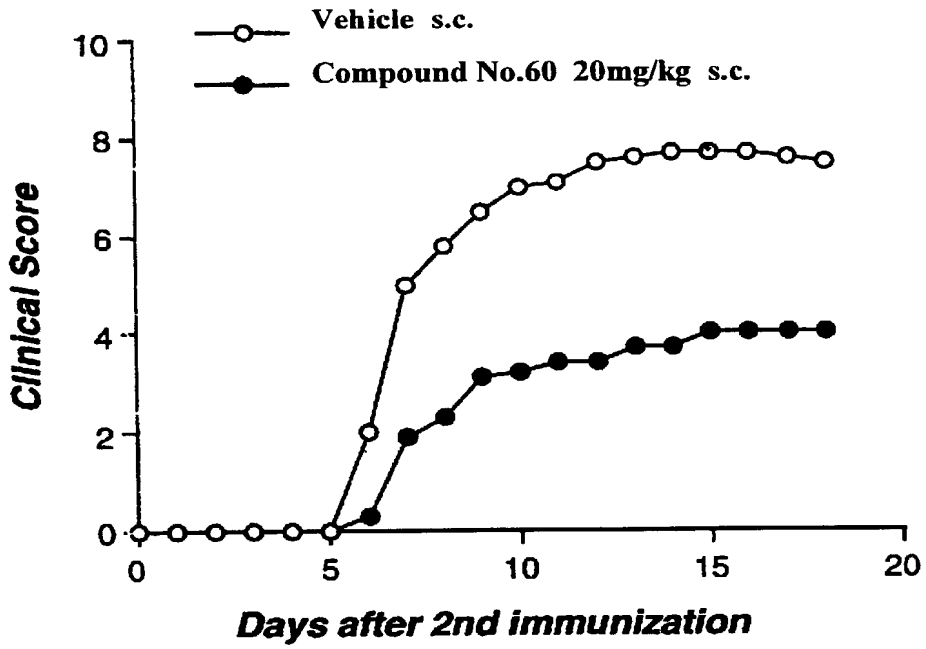

Vehicle s.c.
Compound No.60 20mg/kg s.c.
Clinical Score
10
8
6
4
2
0
0
5
10
15
20
Days after 2nd immunization

Figure 1A

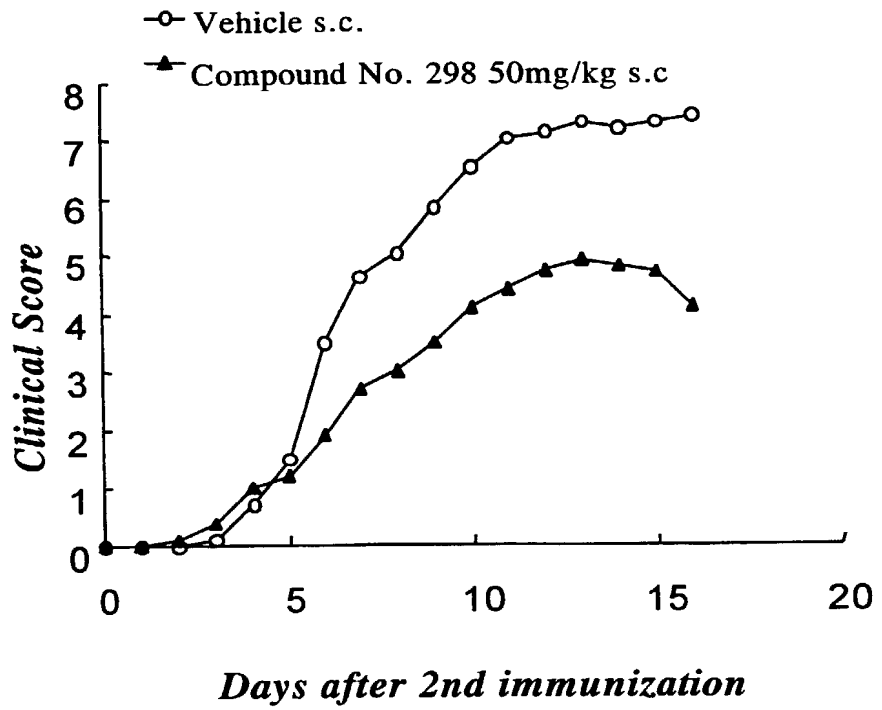

Vehicle s.c.
Compound No. 298 50mg/kg s.c
Clinical Score
0
1
2
3
4
5
6
7
8
0
5
10
15
20
Days after 2nd immunization

Figure 1B

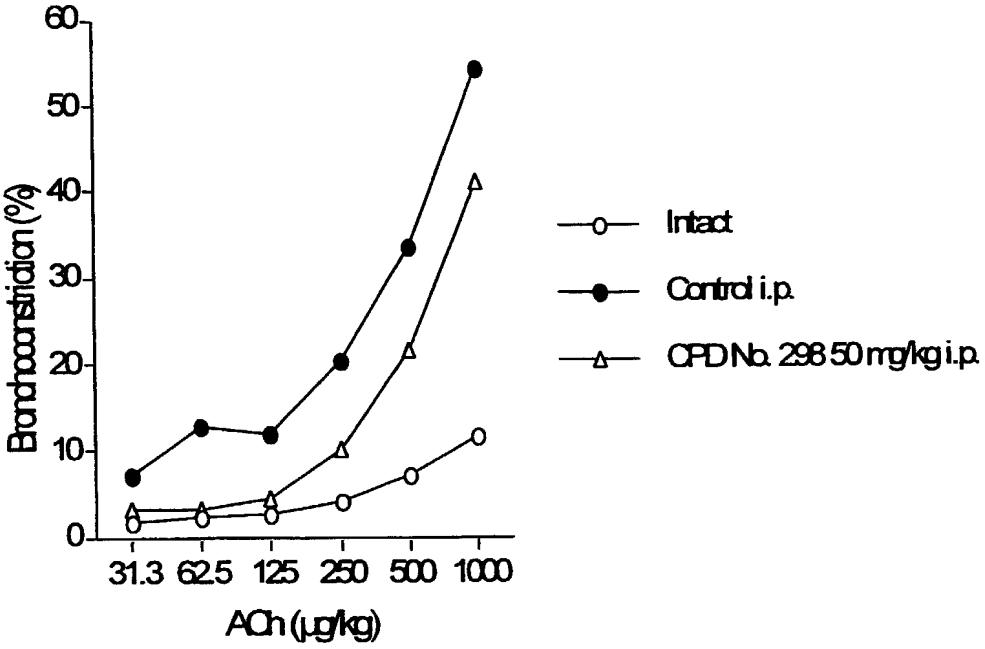

60
50
40
30
20
10
0
Bronchoconstriction (%)
31.3
62.5
125
250
500
1000
ACh (µg/kg)
Intact
Control i.p.
CPD No. 298 50 mg/kg i.p.

Figure 2A

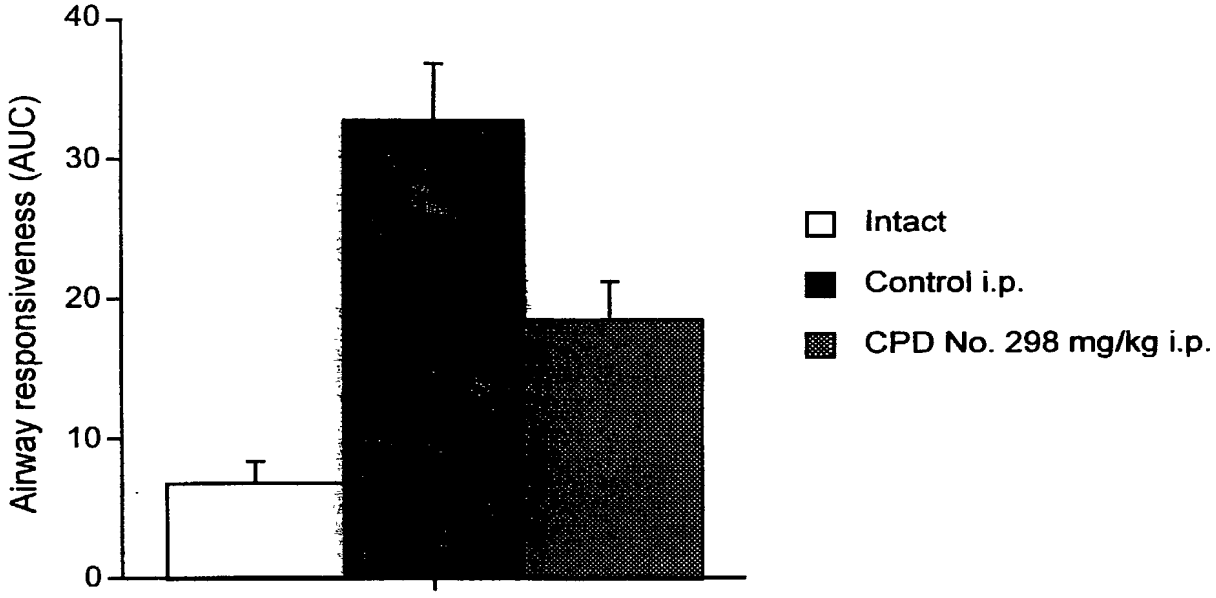

40
30
20
10
0
Airway responsiveness (AUC)
Intact
Control i.p.
CPD No. 298 mg/kg i.p.

Figure 2B

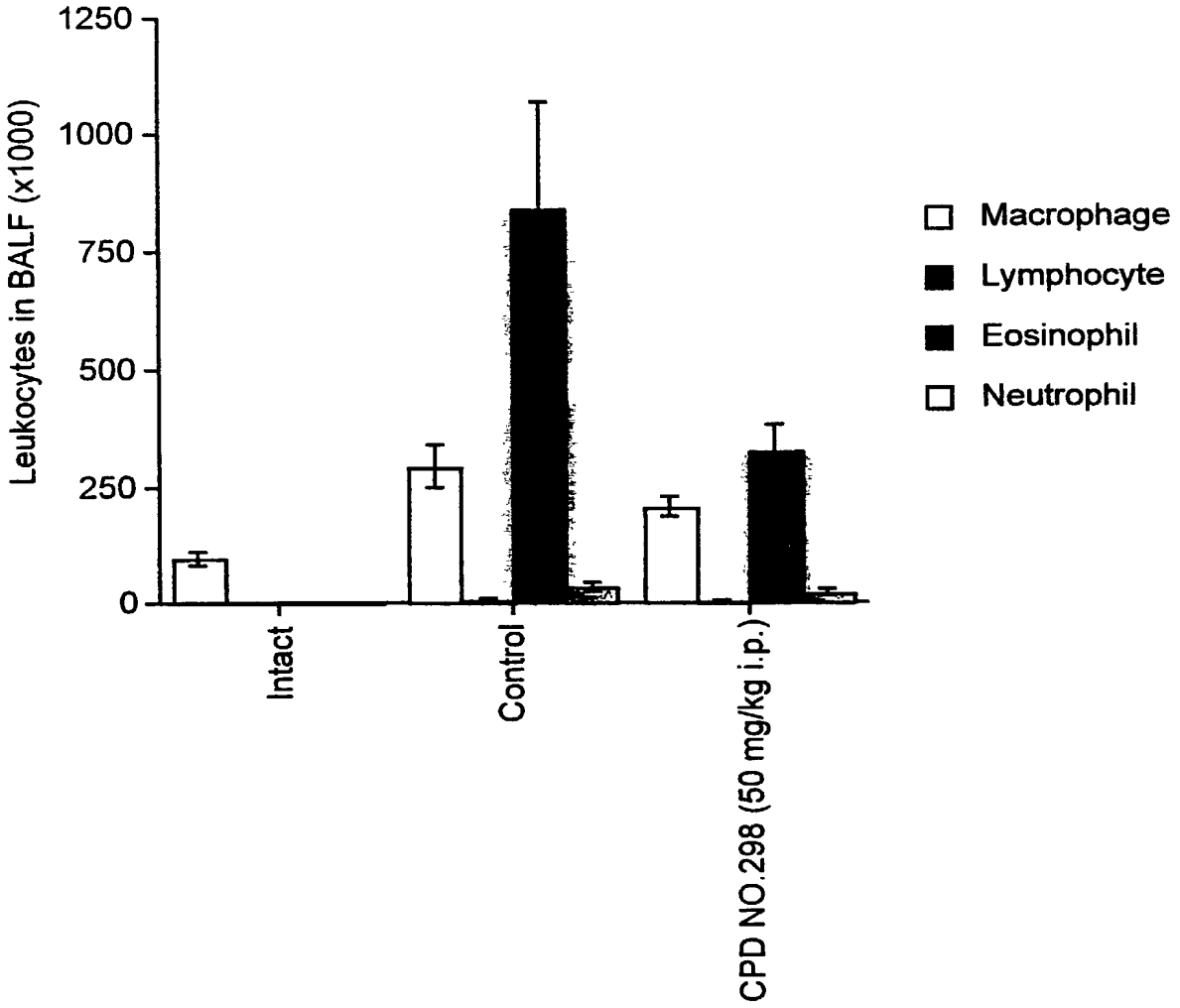

1250
1000
750
500
250
0
Leukocytes in BALF (x1000)
Intact
Control
CPD NO.298 (50 mg/kg i.p.)
Macrophage
Lymphocyte
Eosinophil
Neutrophil

Figure 2C

Atty. Dkt. No. 051023-0111

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

UREA DERIVATIVES AS INHIBITORS FOR CCR-3 RECEPTOR

(Attorney Docket No. 051023-0111)

the specification of which (check one)

___ Is attached hereto.

_X_ Was filed on 02/02/02 as United States Application Number or PCT International Application Number 10/019,652 and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or

Atty. Dkt. No. 051023-0111

of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date
60/191,094	03/22/2000
60/146,219	07/28/1999

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number
	US00/17868	07/28/2000	

I HEREBY APPOINT the following registered attorneys and agents of the law firm of FOLEY & LARDNER:

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to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

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I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Atty. Dkt. No. 051023-0111

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